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Signed this 6th day of February 2009



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FEDERAL REPUBLIC OF GERMANY

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**Priority Certificate
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Title: 6-Cyclylmethyl- and 6-alkylmethyl-substituted pyrazolopyrimidines

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The attached documents are a correct and accurate reproduction of the original submission for this Application.

Munich, 13 February 2004

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The President

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Remus

6-Cyclymethyl- and 6-alkylmethyl-substituted pyrazolopyrimidines

The invention relates to novel 6-cyclymethyl- and 6-alkylmethyl-substituted pyrazolopyrimidines, process for their preparation and their use for producing medicaments for improving perception, concentration, learning and/or memory.

5 Inhibition of phosphodiesterases modulates the levels of the cyclic nucleotides 5'-3' cyclic adenosine monophosphate (cAMP) and 5'-3' cyclic guanosine monophosphate (cGMP). These cyclic nucleotides (cAMP and cGMP) are important second messengers and therefore play a central role in cellular signal transduction cascades. Each of them reactivates inter alia, but not exclusively, protein kinases. The protein kinase activated by cAMP is called protein kinase A
10 (PKA), and the protein kinase activated by cGMP is called protein kinase G (PKG). Activated PKA and PKG are able in turn to phosphorylate a number of cellular effector proteins (e.g. ion channels, G-protein-coupled receptors, structural proteins). It is possible in this way for the second messengers cAMP and cGMP to control a wide variety of physiological processes in a wide variety of organs. However, the cyclic nucleotides are also able to act directly on effector
15 molecules. Thus, it is known, for example, that cGMP is able to act directly on ion channels and thus is able to influence the cellular ion concentration (review in: Wei et al., *Prog. Neurobiol.*, **1998**, 56: 37-64). The phosphodiesterases (PDE) are a control mechanism for controlling the activity of cAMP and cGMP and thus in turn these physiological processes. PDEs hydrolyse the cyclic monophosphates to the inactive monophosphates AMP and GMP. At least 21 PDE genes
20 have now been described (*Exp. Opin. Investig. Drugs* **2000**, 9, 1354-3784). These 21 PDE genes can be divided on the basis of their sequence homology into 11 PDE families (for proposed nomenclature, see <http://depts.washington.edu/pde/Nomenclature.html>). Individual PDE genes within a family are differentiated by letters (e.g. PDE1A and PDE1B). If different splice variants within a gene also occur, this is then indicated by an additional numbering after the letters (e.g.
25 PDE1A1).

Human PDE9A was cloned and sequenced in 1998. The amino acid identity with other PDEs does not exceed 34% (PDE8A) and is never less than 28% (PDE5A). With a Michaelis-Menten constant (Km) of 170 nM, PDE9A has high affinity for cGMP. In addition, PDE9A is selective for cGMP (Km for cAMP = 230 µM). PDE9A has no cGMP binding domain, suggesting allosteric enzyme
30 regulation by cGMP. It was shown in a Western blot analysis that PDE9A is expressed in humans inter alia in testes, brain, small intestine, skeletal muscle, heart, lung, thymus and spleen. The highest expression was found in the brain, small intestine, heart and spleen (Fisher et al., *J. Biol. Chem.*, **1998**, 273 (25): 15559-15564). The gene for human PDE9A is located on chromosome 21q22.3 and comprises 21 exons. To date, 4 alternative splice variants of PDE9A have been

identified (Guipponi et al., *Hum. Genet.*, **1998**, 103: 386-392). Classical PDE inhibitors do not inhibit human PDE9A. Thus, IBMX, dipyridamole, SKF94120, rolipram and vinpocetine show no inhibition on the isolated enzyme in concentrations of up to 100 μ M. An IC_{50} of 35 μ M has been demonstrated for zaprinast (Fisher et al., *J. Biol. Chem.*, **1998**, 273 (25): 15559-15564).

- 5 Murine PDE9A was cloned and sequenced in 1998 by Soderling et al. (*J. Biol. Chem.*, **1998**, 273 (19): 15553-15558). This has, like the human form, high affinity for cGMP with a K_m of 70 nM. Particularly high expression was found in the mouse kidney, brain, lung and heart. Murine PDE9A is not inhibited by IBMX in concentrations below 200 μ M either; the IC_{50} for zaprinast is 29 μ M (Soderling et al., *J. Biol. Chem.*, **1998**, 273 (19): 15553-15558). It has been found that PDE9A is
- 10 strongly expressed in some regions of the rat brain. These include olfactory bulb, hippocampus, cortex, basal ganglia and basal forebrain (Andreeva et al., *J. Neurosci.*, **2001**, 21 (22): 9068-9076). The hippocampus, cortex and basal forebrain in particular play an important role in learning and memory processes.

- As already mentioned above, PDE9A is distinguished by having particularly high affinity for
- 15 cGMP. PDE9A is therefore active even at low physiological concentrations, in contrast to PDE2A (K_m = 10 μ M; Martins et al., *J. Biol. Chem.*, **1982**, 257: 1973-1979), PDE5A (K_m = 4 μ M; Francis et al., *J. Biol. Chem.*, **1980**, 255: 620-626), PDE6A (K_m = 17 μ M; Gillespie and Beavo, *J. Biol. Chem.*, **1988**, 263 (17): 8133-8141) and PDE11A (K_m = 0.52 μ M; Fawcett et al., *Proc. Nat. Acad. Sci.*, **2000**, 97 (7): 3702-3707). In contrast to PDE2A (Murashima et al., *Biochemistry*, **1990**, 29:
- 20 5285-5292), the catalytic activity of PDE9A is not increased by cGMP because it has no GAF domain (cGMP-binding domain via which the PDE activity is allosterically increased) (Beavo et al., *Current Opinion in Cell Biology*, **2000**, 12: 174-179). PDE9A inhibitors may therefore lead to an increase in the baseline cGMP concentration.

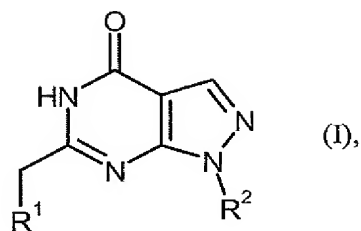
- WO 98/40384 discloses pyrazolopyrimidines which are PDE1, 2 and 5 inhibitors and can be
- 25 employed for the treatment of cardiovascular and cerebrovascular disorders and disorders of the urogenital system.

CH 396 924, CH 396 925, CH 396 926, CH 396 927, DE 1 147 234, DE 1 149 013, GB 937,726 describe pyrazolopyrimidines which have a coronary-dilating effect and which can be employed for the treatment of disturbances of myocardial blood flow.

- 30 US 3,732,225 describes pyrazolopyrimidines which have an antiinflammatory and blood glucose-lowering effect.

DE 2 408 906 describes styrenepyrazolopyrimidines which can be employed as antimicrobial and antiinflammatory agents for the treatment of, for example, oedema.

The present invention relates to compounds of the formula



5 in which

R^1 is C_1 - C_8 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl or C_3 - C_8 -cycloalkyl,

where C_1 - C_8 -alkyl is optionally substituted by oxo, and

where C_1 - C_8 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl and C_3 - C_8 -cycloalkyl are optionally substituted by up to 3 radicals independently of one another selected from the group of
 10 C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, hydroxycarbonyl, cyano, amino, nitro, hydroxy, C_1 - C_6 -alkylamino, halogen, trifluoromethyl, trifluoromethoxy, C_6 - C_{10} -arylcarbonylamino, C_1 - C_6 -alkylcarbonylamino, C_1 - C_6 -alkylaminocarbonyl, C_1 - C_6 -alkoxycarbonyl, C_6 - C_{10} -arylamino-carbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1 - C_6 -alkylsulphonylamino, C_1 - C_6 -alkylsulphonyl, C_1 - C_6 -alkylthio,

15 where

C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -alkylamino, C_6 - C_{10} -arylcarbonylamino, C_1 - C_6 -alkyl-carbonylamino, C_1 - C_6 -alkylaminocarbonyl, C_1 - C_6 -alkoxycarbonyl, C_6 - C_{10} -arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1 - C_6 -alkylsulphonylamino, C_1 - C_6 -alkylsulphonyl and C_1 - C_6 -alkylthio are optionally
 20 substituted by one to three radicals independently of one another selected from the group of hydroxy, cyano, halogen, trifluoromethyl, trifluoromethoxy, hydroxy-carbonyl and a group of the formula $-NR^3R^4$,

where

R^3 and R^4 are independently of one another hydrogen or C_1 - C_6 -alkyl,

25 or

R^3 and R^4 together with the nitrogen atom to which they are bonded are 5- to 8-membered heterocyclyl,

5 R^2 is phenyl or heteroaryl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, trifluoromethoxy, amino, nitro, hydroxy, C_1 - C_6 -alkylamino, halogen, C_6 - C_{10} -arylcarbonylamino, C_1 - C_6 -alkylcarbonylamino, C_1 - C_6 -alkylaminocarbonyl, C_1 - C_6 -alkoxycarbonyl, C_6 - C_{10} -arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1 - C_6 -alkylsulphonylamino, C_1 - C_6 -alkylsulphonyl and C_1 - C_6 -alkylthio,

15 where C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -alkylamino, C_6 - C_{10} -arylcarbonylamino, C_1 - C_6 -alkylcarbonylamino, C_1 - C_6 -alkylaminocarbonyl, C_1 - C_6 -alkoxycarbonyl, C_6 - C_{10} -arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1 - C_6 -alkylsulphonylamino, C_1 - C_6 -alkylsulphonyl and C_1 - C_6 -alkylthio are optionally substituted by one to three radicals independently of one another selected from the group of hydroxy, cyano, halogen, trifluoromethyl, trifluoromethoxy, hydroxycarbonyl and a group of the formula $-NR^3R^4$,

where

R^3 and R^4 have the meanings indicated above,

20 and the salts, solvates and/or solvates of the salts thereof.

Compounds of the invention are the compounds of the formula (I) and the salts, solvates and solvates of the salts thereof; the compounds which are encompassed by formula (I) and have the formulac mentioned hereinafter and the salts, solvates and solvates of the salts thereof, and the compounds which are encompassed by formula (I) and are mentioned hereinafter as exemplary
25 embodiments and the salts, solvates and solvates of the salts thereof, where the compounds which are encompassed by formula (I) and are mentioned hereinafter are not already salts, solvates and solvates of the salts.

The compounds of the invention may, depending on their structure, exist in stereoisomeric forms (enantiomers, diastereomers). The invention therefore relates to the enantiomers or diastereomers
30 and respective mixtures thereof. The sterically pure constituents can be isolated in a known manner from such mixtures of enantiomers and/or diastereomers.

Salts which are preferred for these purposes of the invention are physiologically acceptable salts of the compounds of the invention.

5 Physiologically acceptable salts of the compounds (I) include acid addition salts of mineral acids, carboxylic acids and sulphonic acids, e.g. salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

10 Physiologically acceptable salts of the compounds (I) also include salts of conventional bases such as, by way of example and preferably, alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having 1 to 16 C atoms, such as, by way of example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, dehydroabietylamine, arginine, lysine, ethylenediamine and methylpiperidine.

15 Solvates refers for the purposes of the invention to those forms of the compounds which form, in the solid or liquid state, a complex by coordination with solvent molecules. Hydrates are a specific form of solvates in which the coordination takes place with water.

In addition, the present invention also encompasses prodrugs of the compounds of the invention. The term "prodrugs" encompasses compounds which themselves may be biologically active or inactive
20 but are converted (for example by metabolism or hydrolysis) into compounds of the invention during their residence time in the body.

For the purposes of the present invention, the substituents have the following meaning, unless specified otherwise:

25 C₁-C₈-Alkyl is a straight-chain or branched alkyl radical having 1 to 8, preferably 1 to 6, particularly preferably 1 to 5, carbon atoms. Preferred examples include methyl, ethyl, n-propyl, isopropyl, 2-butyl, 2-pentyl and 3-pentyl.

C₂-C₆-Alkenyl is a straight-chain or branched alkenyl radical having 2 to 6, preferably 2 to 4 and particularly preferably having 2 to 3, carbon atoms. Preferred examples include vinyl, allyl, n-prop-1-en-1-yl and n-but-2-en-1-yl.

C₂-C₆-Alkynyl is a straight-chain or branched alkynyl radical having 2 to 6, preferably having 2 to 4 and particularly preferably having 2 to 3 carbon atoms. Preferred examples include ethynyl, n-prop-1-yn-2-yl, n-prop-1-yn-3-yl and n-but-2-yn-1-yl.

5 C₁-C₆-Alkoxy is a straight-chain or branched alkoxy radical having 1 to 6, preferably 1 to 4, particularly preferably having 1 to 3 carbon atoms. Preferred examples include methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

C₁-C₆-Alkoxycarbonyl is a straight-chain or branched alkoxycarbonyl radical having 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3, carbon atoms. Preferred examples include methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and tert-butoxycarbonyl.

10 C₁-C₆-Alkylamino is a straight-chain or branched mono- or dialkylamino radical having 1 to 6, preferably 1 to 4 and particularly preferably having 1 to 3 carbon atoms. Preferred examples include methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino and n-hexylamino, dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, di-t-butylamino, di-n-pentylamino, di-n-hexylamino, ethylmethylamino, isopropylmethylamino, n-butylethylamino
15 and n-hexyl-i-pentylamino.

C₁-C₆-Alkylcarbonylamino is an alkylcarbonyl radical linked via an amino group, where the alkyl radical may be straight-chain or branched and comprises 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3, carbon atoms. Preferred examples include methylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, isopropylcarbonylamino, tert-butylcarbonylamino,
20 n-pentylcarbonylamino and n-hexylcarbonylamino.

C₁-C₆-Alkylaminocarbonyl is a mono- or dialkylamino radical linked via a carbonyl group, where the alkyl radicals may be identical or different, are straight-chain or branched and each comprise 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3, carbon atoms. Preferred examples include methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, dimethylaminocarbonyl,
25 diethylaminocarbonyl, di-n-propylaminocarbonyl, diisopropylaminocarbonyl, di-t-butylaminocarbonyl, di-n-pentylaminocarbonyl, di-n-hexylaminocarbonyl, ethylmethylaminocarbonyl, isopropylmethylaminocarbonyl, n-butylethylaminocarbonyl and n-hexyl-i-pentylaminocarbonyl. A further possibility in the case of a dialkylamino radical is for the two
30 alkyl radicals to form together with the nitrogen atom to which they are bonded a 5- to 8-membered heterocyclyl.

C₆-C₁₀-Arylaminocarbonyl is an arylamino radical linked via a carbonyl group. Preferred examples include phenylaminocarbonyl and naphthylaminocarbonyl.

C₆-C₁₀-Arylcarbonylamino is an arylamino radical linked via an amino group. Preferred examples include phenylaminocarbonyl and naphthylaminocarbonyl.

- 5 C₁-C₆-Alkylsulphonylamino is a straight-chain or branched alkylsulphonylamino radical having 1 to 6, preferably 1 to 4 and particularly preferably having 1 to 3, carbon atoms. Preferred examples include methylsulphonylamino, ethylsulphonylamino, n-propylsulphonylamino, isopropylsulphonylamino, tert-butylsulphonylamino, n-pentylsulphonylamino and n-hexylsulphonylamino.

- 10 C₁-C₆-Alkylsulphonyl is a straight-chain or branched alkylsulphonyl radical having 1 to 6, preferably 1 to 4 and particularly preferably having 1 to 3, carbon atoms. Preferred examples include methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, tert-butylsulphonyl, n-pentylsulphonyl and n-hexylsulphonyl.

- 15 C₁-C₆-Alkylthio is a straight-chain or branched alkylthio radical having 1 to 6, preferably 1 to 4 and particularly preferably having 1 to 3, carbon atoms. Preferred examples include methylthio, ethylthio, n-propylthio, isopropylthio, tert-butylthio, n-pentylthio and n-hexylthio.

Halogen is fluorine, chlorine, bromine and iodine. Fluorine, chlorine, bromine are preferred, and fluorine and chlorine are particularly preferred.

- 20 Heteroaryl is an aromatic, mono- or bicyclic radical having 5 to 10 ring atoms and up to 5 heteroatoms from the series S, O and/or N. 5- to 6-membered heteroaryls having up to 4 heteroatoms are preferred. The heteroaryl radical may be bonded via a carbon or nitrogen atom. Preferred examples include thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, tetrazolyl, pyridyl, N-oxidopyridyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl and isoquinolinyl.

- 25 Heteroarylaminocarbonyl is a heteroarylamino radical linked via a carbonyl group. Preferred examples include thienylaminocarbonyl, furylaminocarbonyl, pyrrolylaminocarbonyl, thiazolylaminocarbonyl, oxazolylaminocarbonyl, imidazolylaminocarbonyl, tetrazolylaminocarbonyl, pyridylaminocarbonyl, pyrimidinylaminocarbonyl, pyridazinylaminocarbonyl, indolylaminocarbonyl, indazolylaminocarbonyl, benzofuranylaminocarbonyl, benzothiophenylaminocarbonyl, quinolinylaminocarbonyl and isoquinolinylaminocarbonyl.

- 30 Heteroarylcarbonylamino is a heteroarylcarbonyl radical linked via an amino group. Preferred examples include thienylcarbonylamino, furylcarbonylamino, pyrrolylcarbonylamino,

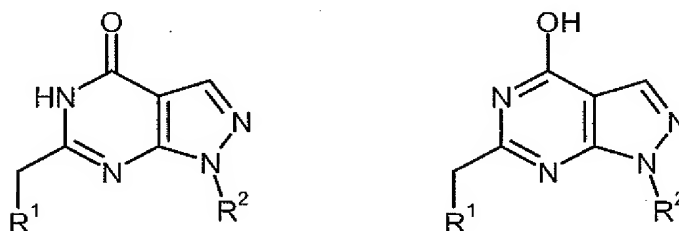
thiazolylcarbonylamino, oxazolylcarbonylamino, imidazolylcarbonylamino, tetrazolylcarbonylamino, pyridylcarbonylamino, pyrimidinylcarbonylamino, pyridazinylcarbonylamino, indolylcarbonylamino, indazolylcarbonylamino, benzofuranylcarbonylamino, benzothiophenylcarbonylamino, quinolinylcarbonylamino and isoquinolinylcarbonylamino.

- 5 3- to 8-membered cycloalkyl stands for saturated and partially unsaturated nonaromatic cycloalkyl radicals having 3 to 8, preferably 3 to 6 and particularly preferably 5 to 6, carbon atoms in the ring. Preferred examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl.

- 10 5- to 8-membered heterocyclyl is a mono- or polycyclic heterocyclic radical having 5 to 8 ring atoms and up to 3, preferably 2, heteroatoms or hetero groups from the series N, O, S, SO, SO₂. Mono- or bicyclic heterocyclyl is preferred. Monocyclic heterocyclyl is particularly preferred. N and O are preferred as heteroatoms. The heterocyclyl radicals may be saturated or partially unsaturated. Saturated heterocyclyl radicals are preferred. 5- to 7-membered heterocyclyl radicals are particularly preferred. Preferred examples include oxetan-3-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, 15 pyrrolinyl, tetrahydrofuranyl, tetrahydrothienyl, pyranyl, piperidinyl, thiopyranyl, morpholinyl, perhydroazepinyl.

When radicals in the compounds of the invention are optionally substituted, unless otherwise specified substitution by up to three identical or different substituents is preferred.

- 20 The compounds of the invention may also be in the form of tautomers as shown by way of example below:



A further embodiment of the invention relates to compounds of the formula (I)

in which

- 25 R¹ is C₁-C₈-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl or C₃-C₈-cycloalkyl, which are optionally substituted by up to 3 radicals independently of one another selected from the group of C₁-C₆-alkyl, C₁-C₆-alkoxy, hydroxycarbonyl, cyano, amino, nitro, hydroxy, C₁-C₆-alkylamino, halogen, C₆-C₁₀-arylcarbonylamino, C₁-C₆-alkylcarbonylamino, C₁-C₆-alkyl-

aminocarbonyl, C₁-C₆-alkoxycarbonyl, C₆-C₁₀-arylaminocarbonyl, heteroaryl-aminocarbonyl, heteroarylcarbonylamino, C₁-C₆-alkylsulphonylamino, C₁-C₆-alkylsulphonyl and C₁-C₆-alkylthio,

where

5 C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkylamino, C₆-C₁₀-arylcarbonylamino, C₁-C₆-alkylcarbonylamino, C₁-C₆-alkylaminocarbonyl, C₁-C₆-alkoxycarbonyl, C₆-C₁₀-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C₁-C₆-alkylsulphonylamino, C₁-C₆-alkylsulphonyl and C₁-C₆-alkylthio are optionally substituted by a radical selected from the group of hydroxy, cyano, halogen,
10 hydroxycarbonyl and a group of the formula -NR³R⁴,

where

R³ and R⁴ are independently of one another hydrogen or C₁-C₆-alkyl,

or

15 R³ and R⁴ together with the nitrogen atom to which they are bonded are 5- to 8-membered heterocyclyl,

R² is phenyl or heteroaryl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C₁-C₆-alkyl, C₁-C₆-alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, nitro, hydroxy, C₁-C₆-alkylamino, halogen, C₆-C₁₀-arylcarbonylamino, C₁-C₆-alkylcarbonylamino, C₁-C₆-alkylaminocarbonyl, C₁-C₆-alkoxycarbonyl, C₆-C₁₀-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C₁-C₆-alkylsulphonylamino, C₁-C₆-alkylsulphonyl, C₁-C₆-alkylthio,
20

where C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkylamino, C₆-C₁₀-arylcarbonylamino, C₁-C₆-alkylcarbonylamino, C₁-C₆-alkylaminocarbonyl, C₁-C₆-alkoxycarbonyl, C₆-C₁₀-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C₁-C₆-alkylsulphonylamino, C₁-C₆-alkylsulphonyl and C₁-C₆-alkylthio are optionally substituted by a radical selected from the group of hydroxy, cyano, halogen, hydroxycarbonyl and a group of formula -NR³R⁴,
25

where

30 R³ and R⁴ have the meanings indicated above,

and the salts, solvates and/or solvates of the salts thereof.

A further embodiment of the invention relates to compounds of the formula (I)

in which

5 R^1 is C_1 - C_5 -alkyl or C_3 - C_6 -cycloalkyl, which are optionally substituted by up to 3 radicals independently of one another selected from the group of C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, trifluoromethyl, hydroxycarbonyl, cyano, amino, hydroxy, C_1 - C_4 -alkylamino, fluorine, chlorine, bromine, C_6 - C_{10} -arylcarbonylamino, C_1 - C_4 -alkylcarbonylamino, C_1 - C_4 -alkylaminocarbonyl, C_1 - C_4 -alkoxycarbonyl, C_6 - C_{10} -arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1 - C_4 -alkylsulphonylamino, C_1 - C_4 -alkylsulphonyl, C_1 - C_4 -alkylthio,

where C_1 - C_4 -alkyl and C_1 - C_4 -alkoxy are optionally substituted by a radical selected from the group of hydroxy, cyano, fluorine, chlorine, bromine, hydroxycarbonyl and a group of the formula $-NR^3R^4$,

where

15 R^3 and R^4 are independently of one another hydrogen or C_1 - C_4 -alkyl,

or

R^3 and R^4 together with the nitrogen atom to which they are bonded are 5- to 6-membered heterocyclyl,

20 R^2 is phenyl, pyrimidyl, N-oxidopyridyl or pyridyl, where phenyl is substituted by 1 to 3 radicals and pyrimidyl, N-oxidopyridyl and pyridyl are optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, hydroxy, C_1 - C_4 -alkylamino, fluorine, chlorine, bromine, C_6 - C_{10} -arylcarbonylamino, C_1 - C_4 -alkylcarbonylamino, C_1 - C_4 -alkylaminocarbonyl, C_1 - C_4 -alkoxycarbonyl, C_6 - C_{10} -arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1 - C_4 -alkylsulphonylamino, C_1 - C_4 -alkylsulphonyl, C_1 - C_4 -alkylthio,

where C_1 - C_4 -alkyl and C_1 - C_4 -alkoxy are optionally substituted by a radical selected from the group of hydroxy, cyano, fluorine, chlorine, bromine, hydroxycarbonyl and a group of the formula $-NR^3R^4$,

where

R^3 and R^4 have the meanings indicated above,

and the salts, solvates and/or solvates of the salts thereof.

A further embodiment of the invention relates to compounds of the formula (I)

5 in which

R^1 has the meanings indicated above, and

R^2 is phenyl, N-oxidopyridyl or pyridyl, where phenyl is substituted by 1 to 3 radicals and pyridyl and N-oxidopyridyl are optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of methyl, ethyl, 2-propyl,
10 trifluoromethyl, methoxy, ethoxy, fluorine and chlorine,

and the salts, solvates and/or solvates of the salts thereof.

A further embodiment of the invention relates to compounds of the formula (I),

in which

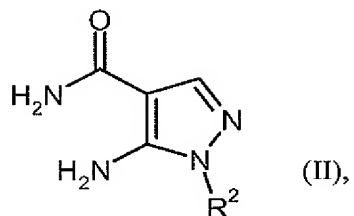
R^1 is C_1 - C_5 -alkyl or C_5 - C_6 -cycloalkyl, which are optionally substituted by up to 3 radicals
15 independently of one another selected from the group of C_1 - C_4 -alkyl, fluorine, trifluoromethyl, hydroxy, phenylcarbonylamino, C_1 - C_4 -alkylcarbonylamino, C_1 - C_4 -alkylaminocarbonyl or phenylaminocarbonyl, and

R^2 is phenyl, N-oxidopyridyl or pyridyl, where phenyl is substituted by 1 to 3 radicals and pyridyl and N-oxidopyridyl are optionally substituted by 1 to 3 radicals in each case
20 independently of one another selected from the group of methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, ethoxy, fluorine and chlorine,

and the salts, solvates and/or solvates of the salts thereof.

A process for preparing compounds of the invention of the formula (I) has also been found, characterized in that either

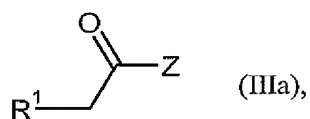
25 [A] compounds of the formula



in which

R^2 has the meanings indicated above,

are converted by reaction with a compound of the formula



5

in which

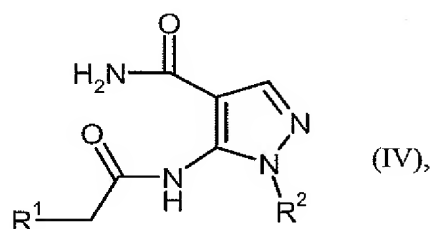
R^1 has the meanings indicated above,

and

Z is chlorine or bromine,

10

in an inert solvent and in the presence of a base, initially into compounds of the formula



in which

R^1 and R^2 have the meanings indicated above,

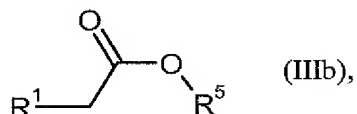
and then cyclized in an inert solvent in the presence of a base to compounds of the formula

15

(I),

or

[B] compounds of the formula (II) are reacted with a compound of the formula



in which

R^1 has the meanings indicated above,

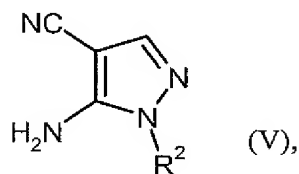
and

5 R^5 is methyl or ethyl,

in an inert solvent and in the presence of a base, with direct cyclization to (I),

or

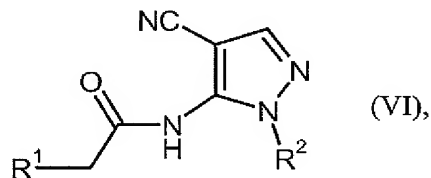
[C] compounds of the formula



10 in which

R^2 has the meanings indicated above,

are converted initially by reaction with a compound of the formula (IIIa) in an inert solvent and in the presence of a base into compounds of the formula



15 in which

R^1 and R^2 have the meanings indicated above,

and the latter are cyclized in a second step in an inert solvent and in the presence of a base and of an oxidizing agent to (I),

and the resulting compounds of the formula (I) are where appropriate reacted with the appropriate (i) solvents and/or (ii) bases or acids to give their solvates, salts and/or solvates of the salts.

Suitable for the first step of process [A] and of process [C] are inert organic solvents which are not changed under the reaction conditions. These preferably include ethers such as, for example, diethyl ether, dioxane, tetrahydrofuran or glycol dimethyl ether, or toluene or pyridine. It is likewise possible to employ mixtures of the solvents mentioned. Tetrahydrofuran, toluene or pyridine are particularly preferred.

Generally suitable bases are alkali metal hydrides such as, for example, sodium hydride, or cyclic amines such as, for example, piperidine, pyridine, dimethylaminopyridine (DMAP) or C₁-C₄-alkylamines such as, for example, triethylamine. Sodium hydride, pyridine and/or dimethylaminopyridine are preferred.

The base is generally employed in an amount of from 1 mol to 4 mol, preferably from 1.2 mol to 3 mol, in each case based on 1 mol of the compounds of the general formula (II) or (V).

In one variant, the reaction is carried out in pyridine to which a catalytic amount of DMAP is added. It is also possible where appropriate to add toluene.

The reaction temperature can generally be varied within a relatively wide range. It is generally in a range from -20°C to +200°C, preferably from 0°C to +100°C.

Solvents suitable for the cyclization in the second step of processes [A] and [C] are the usual organic solvents. These preferably include alcohols such as methanol, ethanol, propanol, isopropanol, n-butanol or tert-butanol, or ethers such as tetrahydrofuran or dioxane, or dimethylformamide or dimethyl sulphoxide. Alcohols such as methanol, ethanol, propanol, isopropanol or tert-butanol are particularly preferably used. It is likewise possible to employ mixtures of the solvents mentioned.

Bases suitable for the cyclization in the second step of processes [A] and [C] are the usual inorganic bases. These preferably include alkali metal hydroxides or alkaline earth metal hydroxides such as, for example, sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal carbonates such as sodium or potassium carbonate or sodium bicarbonate, or alkali metal alcoholates such as sodium methanolate, sodium ethanolate, potassium methanolate, potassium ethanolate or potassium tert-butanolate. Potassium carbonate, sodium hydroxide and potassium tert-butanolate are particularly preferred.

When carrying out the cyclization, the base is generally employed in an amount of from 2 mol to 6 mol, preferably from 3 mol to 5 mol, in each case based on 1 mol of the compounds of the general formula (IV) or (VI).

Oxidizing agents suitable for the cyclization in the second step of process [C] are, for example, hydrogen peroxide or sodium borate. Hydrogen peroxide is preferred.

The cyclization in processes [A], [B] and [C] is generally carried out in a temperature range from 0°C to +160°C, preferably at the boiling point of the particular solvent.

The cyclization is generally carried out under atmospheric pressure. However, it is also possible to carry out the process under elevated pressure or under reduced pressure (e.g. in a range from 0.5 to 5 bar).

Solvents suitable for process [B] are the alcohols mentioned above for the second step of processes [A] and [C], with preference for ethanol.

Bases suitable for process [B] are alkali metal hydrides such as, for example, sodium or potassium hydride, or alkali metal alcoholates such as, for example, sodium methanolate, ethanolate, isopropoxide or potassium tert-butoxide. Sodium hydride is preferred.

The base is employed in an amount of from 2 mol to 8 mol, preferably from 3 mol to 6 mol, in each case based on 1 mol of the compounds of the formula (II).

The compounds of the formula (II) are known or can be prepared for example by initially condensing ethoxymethylenemalononitrile with hydrazine derivatives of the formula (VII)

$$R^2-NH-NH_2 \quad (VII),$$

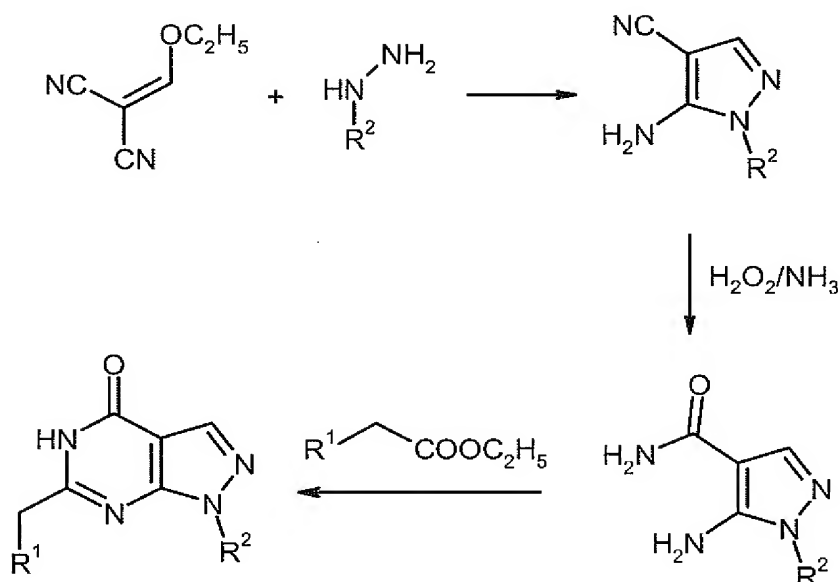
in which

R^2 has the meanings indicated above,

in an inert solvent to give pyrazolenitriles of the formula (V), and then reacting the latter with one of the oxidizing agents mentioned above, preferably hydrogen peroxide, in the presence of ammonia [cf., for example, A. Miyashita et al., *Heterocycles* 1990, 31, 1309ff].

The compounds of the formulae (IIIa), (IIIb) and (VII) are commercially available, known from the literature or can be prepared in analogy to processes known from the literature.

The process of the invention can be illustrated by way of example by the following formula scheme:

Scheme

Further processes for preparing pyrazolo[3,4-d]pyrimidin-4-ones are known and can likewise be employed for synthesizing the compounds of the invention (see, for example: P. Schmidt et al.,
 5 *Helvetica Chimica Acta* **1962**, 189, 1620ff.).

The compounds of the invention show a valuable range of pharmacological and pharmacokinetic effects which could not have been predicted. They are distinguished in particular by inhibition of PDE9A.

They are therefore suitable for use as medicaments for the treatment and/or prophylaxis of diseases
 10 in humans and animals.

For the purposes of the present invention, the term "treatment" includes prophylaxis.

It has surprisingly been found that the compounds of the invention are suitable for producing medicaments for improving perception, concentration, learning or memory.

The compounds of the invention can, by reason of their pharmacological and pharmacokinetic
 15 properties, be employed alone or in combination with other medicaments for improving perception, concentration, learning and/or memory.

The compounds of the invention are particularly suitable for improving perception, concentration, learning or memory after cognitive impairments like those occurring in particular in situations/diseases/syndromes such as mild cognitive impairment, age-associated learning and
 20 memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma,

stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with
5 corticobasal degeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis.

The *in vitro* effect of the compounds of the invention can be shown with the following biological assays:

10 **PDE inhibition**

Recombinant PDE1C (GenBank/EMBL Accession Number: NM_005020, Loughney et al. *J. Biol. Chem.* **1996** 271, 796-806), PDE2A (GenBank/EMBL Accession Number: NM_002599, Rosman et al. *Gene* **1997** 191, 89-95), PDE3B (GenBank/EMBL Accession Number: NM_000922, Miki et al. *Genomics* **1996**, 36, 476-485), PDE4B (GenBank/EMBL Accession Number: NM_002600,
15 Obernolte et al. *Gene*. **1993**, 129, 239-247), PDE5A (GenBank/EMBL Accession Number: NM_001083, Loughney et al. *Gene* **1998**, 216, 139-147), PDE7B (GenBank/EMBL Accession Number: NM_018945, Hetman et al. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, 97, 472-476), PDE8A (GenBank/EMBL Accession Number: AF_056490, Fisher et al. *Biochem. Biophys. Res. Commun.* **1998** 246, 570-577), PDE9A (Fisher et al., *J. Biol. Chem.*, 1998, 273 (25): 15559-15564), PDE10A
20 (GenBank/EMBL Accession Number: NM_06661, Fujishige et al. *J Biol Chem.* **1999**, 274, 18438-45), PDE11A (GenBank/EMBL Accession Number: NM_016953, Fawcett et al. *Proc. Natl. Acad. Sci.* **2000**, 97, 3702-3707) were expressed in Sf9 cells with the aid of the pFASTBAC baculovirus expression system (GibcoBRL).

The test substances are dissolved in 100% DMSO and serially diluted to determine their *in vitro*
25 effect on PDE 9A. Typically, serial dilutions from 200 μ M to 1.6 μ M are prepared (resulting final concentrations in the assay: 4 μ M to 0.032 μ M). 2 μ L portions of the diluted substance solutions are introduced into the wells of microtiter plates (Isoplate; Wallac Inc., Atlanta, GA). Then 50 μ L of a dilution of the PDE9A preparation described above are added. The dilution of the PDE9A preparation is chosen so that less than 70% of the substrate is converted during the subsequent
30 incubation (typical dilution: 1:10000; dilution buffer: 50 mM Tris/HCl pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EDTA, 0.2% BSA). The substrate, [8- 3H] guanosine 3',5'-cyclic phosphate (1 μ Ci/ μ L; Amersham Pharmacia Biotech., Piscataway, NJ) is diluted 1:2000 with assay buffer (50 mM Tris/HCl pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EDTA) to a concentration of 0.0005 μ Ci/ μ L. The enzyme reaction is finally started by adding 50 μ L (0.025 μ Ci) of the diluted substrate. The assay

mixtures are incubated at room temperature for 60 min and the reaction is stopped by adding 25 μ l of a PDE9A inhibitor (e.g. the inhibitor from preparation example 1, final concentration 10 μ M) dissolved in assay buffer. Immediately thereafter, 25 μ L of a suspension containing 18 mg/mL Yttrium Scintillation Proximity Beads (Amersham Pharmacia Biotech., Piscataway, NJ) are added.

- 5 The microtiter plates are sealed with a film and left to stand at room temperature for 60 min. The plates are then measured for 30 s per well in a Microbeta scintillation counter (Wallac Inc., Atlanta, GA). IC_{50} values are determined from the graphical plot of the substance concentration versus the percentage inhibition.

- Representative examples of the inhibiting effect of the compounds of the invention on PDE9A are
10 listed by means of the IC_{50} values in Table 1:

Table 1

| Example | IC ₅₀ [nM] |
|---------|-----------------------|
| 2 | 38 |
| 5 | 12 |
| 11 | 5 |
| 34 | 12 |
| 37-1 | 60 |
| 38 | 13 |
| 39-1 | 30 |

The *in vitro* effect of test substances on recombinant PDE3B, PDE4B, PDE7B, PDE8A, PDE10A and PDE11A is determined in accordance with the assay protocol described above for PDE 9A with the following adaptations: [5',8-³H] adenosine 3',5'-cyclic phosphate (1 μ Ci/ μ L; Amersham Pharmacia Biotech., Piscataway, NJ) is used as substrate. Addition of an inhibitor solution to stop the reaction is unnecessary. Instead, the incubation of substrate and PDE is followed immediately by addition of the yttrium scintillation proximity beads as described above and thus the reaction is stopped. To determine a corresponding effect on recombinant PDE1C, PDE2A and PDE5A, the protocol is additionally adapted as follows: with PDE1C, additionally 10^{-7} M calmodulin and 3 mM CaCl₂ are added to the reaction mixture. PDE2A is stimulated in the assay by adding 1 μ M cGMP and is assayed with a BSA concentration of 0.01%. The substrate employed for PDE1C and PDE2A is [5',8-³H] adenosine 3',5'-cyclic phosphate (1 μ Ci/ μ L; Amersham Pharmacia Biotech., Piscataway, NJ), and for PDE5A is [8-³H] guanosine 3',5'-cyclic phosphate (1 μ Ci/ μ L; Amersham Pharmacia Biotech., Piscataway, NJ).

Long-term potentiation

Long-term potentiation is regarded as a cellular correlate of learning and memory processes. The following method can be used to determine whether PDE 9 inhibition has an influence on long-term potentiation:

Rat hippocampi are placed at an angle of about 70 degrees to the cutting blade (chopper). 400 μ m-thick slices of the hippocampus are prepared. The slices are removed from the blade using a very soft, thoroughly wetted brush (martin hair) and transferred into a glass vessel with cold nutrient solution (124 mM NaCl, 4.9 mM KCl, 1.3 mM MgSO₄ \times 7 H₂O, 2.5 mM CaCl₂ anhydrous, 1.2 mM KH₂PO₄, 25.6 mM NaHCO₃, 10 mM glucose, pH 7.4) gassed with 95% O₂/5% CO₂. During the measurement, the slices are kept in a temperature-controlled chamber under a 1-3 mm-high

liquid level. The flow rate is 2.5 ml/min. The preliminary gassing takes place under a slightly elevated pressure (about 1 atm) and through a microneedle in the prechamber. The slice chamber is connected to the prechamber in such a way that a minicirculation can be maintained. The minicirculation is driven by the 95% O₂/5% CO₂ flowing out through the microneedle. The freshly prepared hippocampus slices are adapted in the slice chamber at 33°C for at least 1 hour.

The stimulus level is chosen so that the focal excitatory postsynaptic potentials (fEPSP) are 30% of the maximum excitatory postsynaptic potential (EPSP). A monopolar stimulation electrode consisting of lacquered stainless steel, and a constant-current biphasic stimulus generator (AM Systems 2100) are used for local stimulation of the Schaffer collaterals (voltage: 1-5 V, pulse width of one polarity 0.1 ms, total pulse 0.2 ms). Glass electrodes (borosilicate glass with filament, 1-5 MOhm, diameter: 1.5 mm, tip diameter: 3-20 µm), filled with normal nutrient solution, are used to record the excitatory postsynaptic potentials (fEPSP) from the stratum radiatum. The field potentials are measured versus a chlorinated silver reference electrode located at the edge of the slice chamber using a DC voltage amplifier. The field potentials are filtered through a low-pass filter (5 kHz). The slope of the fEPSPs (fEPSP slope) is determined for the statistical analysis of the experiments. The recording, analysis and control of the experiment takes place with the aid of a software program (PWIN) which was developed in the Department of Neurophysiology. The formation of the average fEPSP slopes at the respective time points and construction of the diagrams takes place with the aid of the EXCEL software, with automatic data recording by an appropriate macro.

Superfusion of the hippocampus slices with a 10 µM solution of the compounds of the invention leads to a significant increase in the LTP.

The *in vivo* effect of the compounds of the invention can be shown for example as follows:

Social recognition test

The social recognition test is a learning and memory test. It measures the ability of rats to distinguish between known and unknown members of the same species. This test is therefore suitable for examining the learning- or memory-improving effect of the substances of the invention.

Adult rats housed in groups are placed singly in test cages 30 min before the start of the test. Four min before the start of the test, the test animal is put in an observation box. After this adaptation time, a juvenile animal is put in with the test animal and the absolute time for which the adult animal inspects the young one is measured for 2 min (trial 1). All behaviours clearly directed at the

young animal are measured, i.e. anogenital inspection, pursuit and grooming, during which the old animal was no further than 1 cm from the young animal. The juvenile is then removed, and the adult is treated with a compound of the invention or vehicle and subsequently returned to its own cage. The test is repeated after a retention time of 24 hours (trial 2). A diminished social
5 interaction time compared with trial 1 indicates that the adult rat remembers the young animal.

The adult animals receive intraperitoneal injections either at a fixed time interval (e.g. 1 hour) before trial 1 or directly following trial 1 either with vehicle (10% ethanol, 20% Solutol, 70% physiological saline) or 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg or 3.0 mg/kg compound of the invention dissolved in 10% ethanol, 20% Solutol, 70% physiological saline. Vehicle-treated rats show no
10 reduction in the social interaction time in trial 2 compared with trial 1. They have consequently forgotten that they have already had contact with the young animal. Surprisingly, the social interaction time in the second run after treatment with the compounds of the invention is significantly reduced compared with those treated with vehicle. This means that the substance-treated rats have remembered the juvenile animal and thus the compounds of the invention display an improving
15 effect on learning and memory.

The present invention further relates to the use of the compounds of the invention for the treatment and/or prophylaxis of disorders, in particular of the aforementioned disorders.

The present invention further relates to the use of the compounds of the invention for producing a
20 medicament for the treatment and/or prophylaxis of disorders, in particular of the aforementioned disorders.

The present invention further relates to a method for the treatment and/or prophylaxis of disorders, in particular of the aforementioned disorders, using an effective amount of the compounds of the
25 invention.

The present invention further relates to medicaments comprising at least one compound of the invention and one or more other active ingredients, in particular for the treatment and/or prophylaxis of the aforementioned disorders.
30

The compounds of the invention may have systemic and/or local effects. They can for this purpose be administered in a suitable way, such as, for example, by the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, dermal, transdermal, conjunctival or otic route or as implant or stent.
35

The compounds of the invention can be administered in suitable administration forms for these administration routes.

Administration forms suitable for oral administration are those which function according to the state of the art and deliver the compounds of the invention in a rapid and/or modified way, and which contain the compounds of the invention in crystalline and/or amorphized and/or dissolved form, such as, for example, tablets (uncoated or coated tablets, for example with coatings which are resistant to gastric juice or dissolve slowly or are insoluble and which control the release of the compound of the invention), tablets which rapidly disintegrate in the mouth, or films/wafers, films/lyophilisates, capsules (for example hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can take place with avoidance of an absorption step (e.g. intravenous, intraarterial, intracardiac, intraspinal or intralumbar) or with inclusion of an absorption (e.g. intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). Administration forms suitable for parenteral administration are, inter alia, injection and infusion preparations in the form of solutions, suspensions, emulsions, lyophilisates or sterile powders.

Examples suitable for other administration routes are medicinal forms for inhalation (inter alia powder inhalators, nebulizers), nasal drops, solutions, sprays; tablets for lingual, sublingual or buccal administration, films/wafers or capsules, suppositories, preparations for the ears or eyes, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (such as, for example, patches), milk, pastes, foams, dusting powders, implants or stents.

The compounds of the invention can be converted into the stated administration forms. This can take place in a manner known per se by mixing with inert, non-toxic, pharmaceutically suitable excipients. These excipients include, inter alia, carriers (for example microcrystalline cellulose, lactose, mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersants or wetting agents (for example sodium dodecyl sulphate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (e.g. antioxidants such as, for example, ascorbic acid), colours (e.g. inorganic pigments such as, for example, iron oxides) and masking tastes and/or odours.

The present invention further relates to medicaments which comprise at least one compound of the invention, normally together with one or more inert, non-toxic, pharmaceutically suitable excipients, and to the use thereof for the aforementioned purposes.

It has generally proved advantageous on parenteral administration to administer amounts of about 0.001 to 10 mg/kg of body weight per day to achieve effective results. The amount per day on oral administration is about 0.005 to 3 mg/kg of body weight.

5 It may nevertheless be necessary to deviate from the stated amounts, in particular as a function of body weight, administration route, individual behaviour towards the active ingredient, type of preparation and time or interval over which administration takes place. Thus, it may in some cases be sufficient to make do with less than the aforementioned minimum amount, whereas in other cases the stated upper limit must be exceeded. Where larger amounts are administered, it may be advisable to divide them into a plurality of single doses over the day.

10

The percentage data in the following tests and examples are, unless indicated otherwise, percentages by weight; parts are parts by weight. Solvent ratios, dilution ratios and concentration data for liquid/liquid solutions are in each case based on volume.

Abbreviations:

| | |
|----------------|-------------------------------------------------------|
| BSA | bovine serum albumin |
| DCI | direct chemical ionization (in MS) |
| DMSO | dimethyl sulphoxide |
| EDTA | ethylenediaminetetraacetic acid |
| ESI | electrospray ionization (in MS) |
| h | hour(s) |
| HPLC | high pressure, high performance liquid chromatography |
| LC-MS | coupled liquid chromatography-mass spectroscopy |
| min | minute(s) |
| m.p. | melting point |
| MS | mass spectroscopy |
| NMR | nuclear magnetic resonance spectroscopy |
| R _t | retention time (in HPLC) |
| Tris | tris(hydroxymethyl)aminomethane |
| TLC | thin-layer chromatography |

LC-MS methods:**Method 1**

- 5 MS apparatus type: Micromass ZQ; HPLC apparatus type: TSP P4000, TSP AS300, TSP UV3000; column: Grom-Sil 120 ODS-4 HE, 50 x 2 mm, 3.0 µm; eluent A: water + 250 µl of 50% strength formic acid / l, eluent B: acetonitrile + 250 µl of 50% strength formic acid / l; gradient: 0.0 min 0% B → 0.2 min 0% B → 2.9 min 70% B → 3.1 min 90% B → 4.5 min 90% B; oven: 50°C; flow rate: 0.8 ml/min; UV detection: 210 nm.

10 **Method 2**

- Instrument: Micromass Platform LCZ with HPLC Agilent Series 1100; column: Grom-Sil 120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; eluent A: 1 l of water + 1 ml of 50% strength formic acid, eluent B: 1 l of acetonitrile + 1 ml of 50% formic acid; gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 4.5 min 10% A; oven: 55°C; flow rate: 0.8 ml/min; UV
15 detection: 208-400 nm.

Method 3

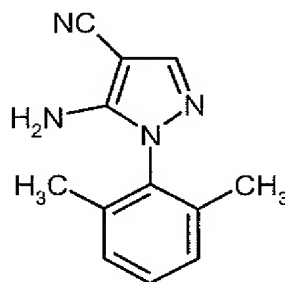
MS apparatus type: Micromass ZQ; HPLC apparatus type: Waters Alliance 2790; column: Grom-Sil 120 ODS-4 HE, 50 x 2 mm, 3.0 µm; eluent B: acetonitrile + 0.05% formic acid, eluent A: water + 0.05% formic acid; gradient: 0.0 min 5% B → 2.0 min 40% B → 4.5 min 90% B → 5.5 min 90% B; oven: 45°C; flow rate: 0.0 min 0.75 ml/min → 4.5 min 0.75 ml/min → 5.5 min 1.25 ml/min; UV detection: 210 nm.

Method 4

Instrument: Micromass Quattro LCZ, with HPLC Agilent Series 1100; column: Grom-Sil 120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; eluent A: 1 l water + 1 ml 50% strength formic acid, eluent B: 1 l acetonitrile + 1 ml 50% strength formic acid; gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 4.5 min 10% A; oven: 55°C; flow rate: 0.8 ml/min; UV detection: 208-400 nm.

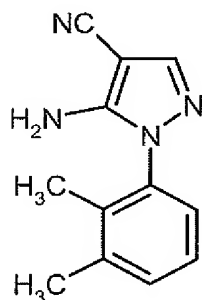
Starting compounds:**Example 1A**

5-Amino-1-(2,6-dimethylphenyl)-1H-pyrazole-4-carbonitrile



3.0 g (17.3 mmol) of 2,6-dimethylphenylhydrazine hydrochloride are suspended with 2.1 g
5 (17.3 mmol) of ethoxymethylenemalononitrile in 40 ml of ethanol, and 7.3 ml (52.1 mmol) of triethylamine are added. The reaction mixture is heated to reflux for 3 h, during which a clear solution forms. After cooling to room temperature, diethyl ether is added. The triethylammonium chloride which precipitates is filtered off. The solvent is removed in vacuo, and the residue is purified by preparative HPLC (YMC gel ODS-AQ S 5/15 μ m; eluent A: water, eluent B: acetonitrile; gradient: 0 min 30% B, 5 min 30% B, 50 min 95% B). 2.3 g (62% of theory) of the
10 product are obtained as yellow crystals.

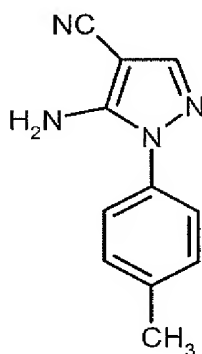
LC-MS (Method 1): $R_t = 2.77$ min.MS (ESI pos): $m/z = 213$ ($M+H$)⁺.

Example 2A**5-Amino-1-(2,3-dimethylphenyl)-1H-pyrazole-4-carbonitrile**

In analogy to the preparation of Example 1A, 2.08 g (56% of theory) of the desired product are obtained starting from 3 g (17.4 mmol) of 2,3-dimethylphenylhydrazine hydrochloride, 2.12 g (17.4 mmol) of ethoxymethylenemalononitrile and 7.3 ml (52.1 mmol) of triethylamine.

LC-MS (Method 1): $R_t = 2.79$ min.

5 MS (ESI pos): $m/z = 213$ ($M+H$)⁺.

Example 3A**5-Amino-1-(4-methylphenyl)-1H-pyrazole-4-carbonitrile**

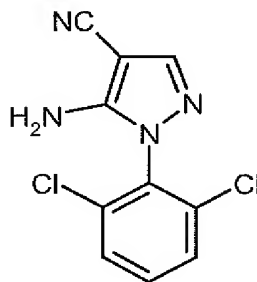
In analogy to the preparation of Example 1A, 2.16 g (57% of theory) of the desired product are obtained starting from 3 g (18.9 mmol) of 4-methylphenylhydrazine hydrochloride, 2.3 g (18.9 mmol) of ethoxymethylenemalononitrile and 7.9 ml (56.7 mmol) of triethylamine.

LC-MS (Method 2): $R_t = 3.0$ min.

MS (ESI pos): $m/z = 199$ ($M+H$)⁺.

Example 4A

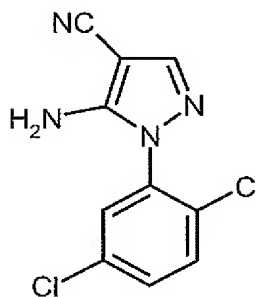
5-Amino-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonitrile



In analogy to the preparation of Example 1A, 2.9 g (83% of theory) of the desired product are obtained starting from 3 g (14.1 mmol) of 2,6-dichlorophenylhydrazine hydrochloride, 1.7 g (14.1 mmol) of ethoxymethylenemalononitrile and 5.8 ml (42.2 mmol) of triethylamine after purification by column chromatography (mobile phase dichloromethane/methanol 98:2).

LC-MS (Method 3): $R_t = 2.8$ min.MS (ESI pos): $m/z = 253$ ($M+H$)⁺¹H-NMR (300 MHz, DMSO- d_6): $\delta = 6.82$ (s, 2H), 7.59 (m, 2H), 7.69 (m, 1H), 7.80 (s, 1H) ppm.10 **Example 5A**

5-Amino-1-(2,5-dichlorophenyl)-1H-pyrazole-4-carbonitrile

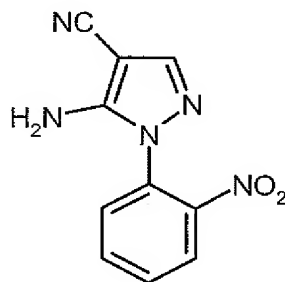


In analogy to the preparation of Example 1A, 2.2 g (51% of theory) of the desired product are obtained starting from 3 g (16.9 mmol) of 2,5-dichlorophenylhydrazine, 2.0 g (16.9 mmol) of ethoxymethylenemalononitrile and 7.1 ml (50.8 mmol) of triethylamine.

LC-MS (Method 2): $R_t = 3.2$ min.MS (ESI pos): $m/z = 253$ ($M+H$)⁺.

Example 6A

5-Amino-1-(2-nitrophenyl)-1H-pyrazole-4-carbonitrile



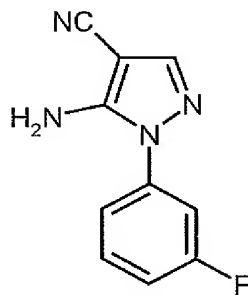
In analogy to the preparation of Example 1A, 1.9 g (53% of theory) of the desired product are
5 obtained starting from 3 g (15.8 mmol) of 2-nitrophenylhydrazine hydrochloride, 1.93 g
(16.9 mmol) of ethoxymethylenemalononitrile and 6.6 ml (47.6 mmol) of triethylamine.

LC-MS (Method 2): $R_t = 2.8$ min.MS (ESI pos): $m/z = 230$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO- d_6): $\delta = 6.87$ (s, 2H), 7.72 (m, 1H), 7.77 (s, 1H), 7.78 (m, 1H), 7.88
10 (m, 1H), 8.16 (dd, 1H) ppm.

Example 7A

5-Amino-1-(3-fluorophenyl)-1H-pyrazole-4-carbonitrile



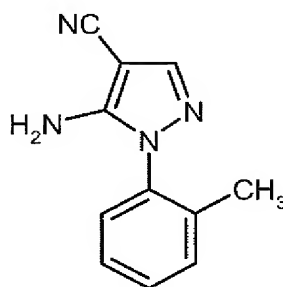
In analogy to the preparation of Example 1A, 1.5 g (31% of theory) of the desired product are
15 obtained starting from 4 g (24.6 mmol) of 3-fluorophenylhydrazine hydrochloride, 3 g (24.6 mmol)
of ethoxymethylenemalononitrile and 10.3 ml (73.8 mmol) of triethylamine.

LC-MS (Method 2): $R_t = 2.9$ min.MS (ESI pos): $m/z = 203$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): δ = 6.81 (s, 2H), 7.28 (m, 1H), 7.36 (m, 2H), 7.57 (m, 1H), 7.80 (s, 1H) ppm.

Example 8A

5-Amino-1-(2-methylphenyl)-1H-pyrazole-4-carbonitrile



5

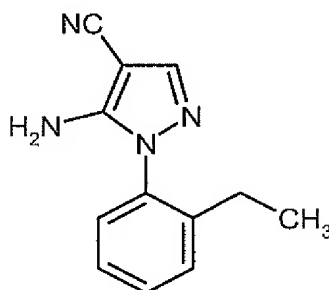
10.2 g (64.4 mmol) of 2-methylphenylhydrazine hydrochloride are suspended with 7.8 g (64.4 mmol) of ethoxymethylenemalononitrile in 100 ml of methanol, and 26.9 ml (193.3 mmol) of triethylamine are added. The reaction mixture is heated to reflux overnight, during which a clear solution forms. The solution is subsequently distilled off under reduced pressure, and the crude product is purified by column chromatography (silica gel, mobile phase dichloromethane). 10.8 g (85% of theory) of the desired product are obtained.

LC-MS (Method 2): R_t = 3.10 min.

MS (ESI pos): m/z = 199 (M+H)⁺.

Example 9A

15 5-Amino-1-(2-ethylphenyl)-1H-pyrazole-4-carbonitrile



In analogy to the preparation of Example 1A, 3.05 g (83.5% of theory) of the desired product are obtained starting from 3.0 g (17.0 mmol) of 2-ethylphenylhydrazine hydrochloride, 2.12 g (17.0 mmol) of ethoxymethylenemalononitrile and 7.1 ml (51.1 mmol) of triethylamine.

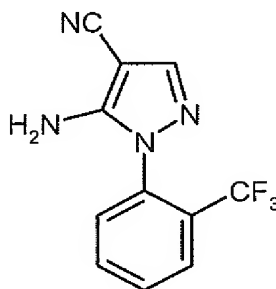
m.p.: 130°C

MS (ESI pos): $m/z = 213$ (M+H)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.0$ (t, 3H), 2.35 (q, 2H), 6.4 (s, 2H), 7.2-7.5 (m, 4H), 7.7 (s, 1H) ppm.

5 **Example 10A**

5-Amino-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonitrile



In analogy to the preparation of Example 1A, 5.02 g (76.9% of theory) of the desired product are obtained starting from 4.8 g (25.9 mmol) of 2-trifluoromethylphenylhydrazine hydrochloride,
10 3.16 g (25.9 mmol) of ethoxymethylenemalononitrile and 7.2 ml (51.7 mmol) of triethylamine.

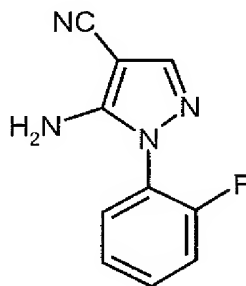
m.p.: 190°C

MS (ESI pos): $m/z = 253$ (M+H)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 6.6$ (s, 2H), 7.5 (d, 1H), 7.7-8.0 (m, 4H) ppm.

Example 11A

5-Amino-1-(2-fluorophenyl)-1H-pyrazole-4-carbonitrile



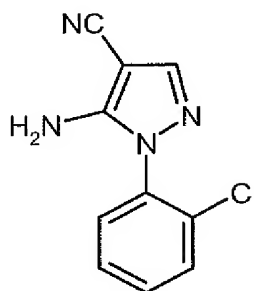
In analogy to the preparation of Example 1A, 5.13 g (88% purity, 84% of theory) of the desired product are obtained starting from 5.0 g (30.8 mmol) of 2-fluorophenylhydrazine hydrochloride, 3.27 g (26.7 mmol) of ethoxymethylenemalononitrile and 11.3 ml (81.3 mmol) of triethylamine.

MS (ESI pos): $m/z = 203$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-*d*₆): $\delta = 6.7$ (s, 2H), 7.3-7.6 (m, 4H), 7.8 (s, 1H) ppm.

Example 12A

10 5-Amino-1-(2-chlorophenyl)-1H-pyrazole-4-carbonitrile



In analogy to the preparation of Example 1A, 4.64 g (78% of theory) of the desired product are obtained starting from 5.0 g (27.1 mmol) of 2-chlorophenylhydrazine hydrochloride, 3.31 g (27.1 mmol) of ethoxymethylenemalononitrile and 11.3 ml (81.3 mmol) of triethylamine.

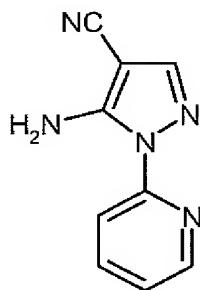
15 m.p.: 135°C

MS (ESI pos): $m/z = 219$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-*d*₆): $\delta = 6.6$ (s, 2H), 7.45-7.75 (m, 4H), 7.8 (s, 1H) ppm.

Example 13A

5-Amino-1-(2-pyridinyl)-1H-pyrazole-4-carbonitrile



In analogy to the preparation of Example 1A, 2.3 g (46.6% of theory) of the desired product are
5 obtained starting from 3.0 g (26.7 mmol, 97% purity) of 2-hydrazinopyridine, 3.26 g (26.7 mmol)
of ethoxymethylenemalononitrile and 7.4 ml (53.3 mmol) of triethylamine.

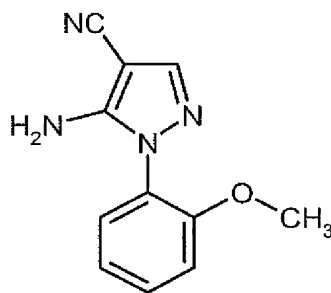
m.p.: 193°C

MS (ESI pos): $m/z = 186 (M+H)^+$

¹H-NMR (300 MHz, DMSO- d_6): $\delta = 7.35$ (m, 1H), 7.8-8.12 (m, 3H), 8.15 (s, 2H), 8.5 (m, 1H)
10 ppm.

Example 14A

5-Amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carbonitrile



In analogy to the preparation of Example 1A, 3.5 g (88% of theory) of the desired product are
15 obtained starting from 4.1 g (18 mmol) of 2-methoxyphenylhydrazine hydrochloride, 2.19 g
(18 mmol) of ethoxymethylenemalononitrile and 10 ml (71.9 mmol) of triethylamine.

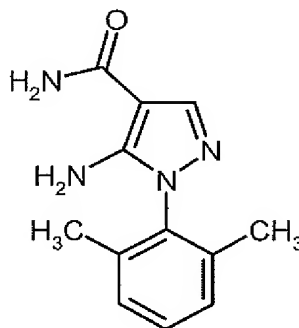
m.p.: 129°C

MS (ESI pos): $m/z = 215 (M+H)^+$

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ = 3.8 (s, 3H), 6.3 (s, 2H), 7.05 (t, 1H), 7.2 (d, 1H), 7.25 (d, 1H), 7.5 (t, 1H), 7.7 (s, 1H) ppm.

Example 15A

5-Amino-1-(2,6-dimethylphenyl)-1H-pyrazole-4-carboxamide



5

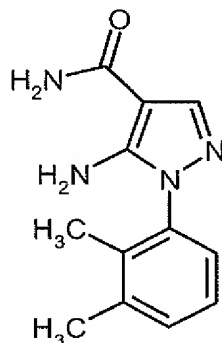
2 g (9.4 mmol) of 5-amino-1-(2,6-dimethylphenyl)-1H-pyrazole-4-carbonitrile (Example 1A) are dissolved in 25 ml of ethanol, and a mixture of 20 ml of 30% strength hydrogen peroxide and 40 ml of 25% strength ammonia is added. The solution is stirred at room temperature overnight and then concentrated to about 15 ml in a rotary evaporator. The oily emulsion resulting thereby is taken up in dichloromethane. It is washed several times with water and saturated sodium thiosulphate solution. Drying over magnesium sulphate is followed by removal of the solvent in vacuo. The residue is purified by preparative HPLC (YMC Gel ODS-AQ S 5/15 μm ; eluent A: water, eluent B: acetonitrile; gradient: 0 min 30% B, 5 min 30% B, 50 min 95% B). 0.88 g (40% of theory) of the product is obtained as colourless solid.

15 LC-MS (Method 2): R_t = 2.6 min.

MS (ESI pos): m/z = 231 ($\text{M}+\text{H}$) $^+$.

Example 16A

5-Amino-1-(2,3-dimethylphenyl)-1H-pyrazole-4-carboxamide



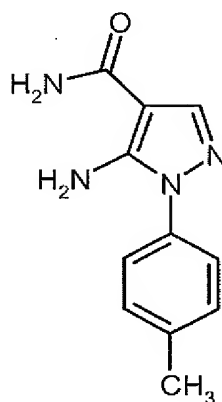
5 In analogy to the preparation of Example 15A, 1.29 g (70% of theory) of the desired product are obtained from 1.5 g (7.1 mmol) of 5-amino-1-(2,3-dimethylphenyl)-1H-pyrazole-4-carbonitrile (Example 2A) in a mixture of 25 ml of ethanol, 10 ml of 30% strength hydrogen peroxide and 40 ml of 25% strength ammonia.

LC-MS (Method 2): $R_t = 2.7$ min.

MS (ESI pos): $m/z = 231$ ($M+H$)⁺.

Example 17A

10 5-Amino-1-(4-methylphenyl)-1H-pyrazole-4-carboxamide



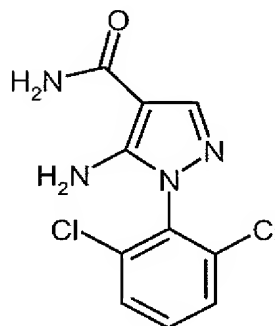
15 In analogy to the preparation of Example 15A, 1.02 g (47% of theory) of the desired product are obtained from 2 g (10.1 mmol) of 5-amino-1-(4-methylphenyl)-1H-pyrazole-4-carbonitrile (Example 3A) in a mixture of 25 ml of ethanol, 20 ml of 30% strength hydrogen peroxide and 40 ml of 25% strength ammonia.

LC-MS (Method 2): $R_t = 2.7$ min.

MS (ESI pos): $m/z = 217$ ($M+H$)⁺.

Example 18A

5-Amino-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carboxamide



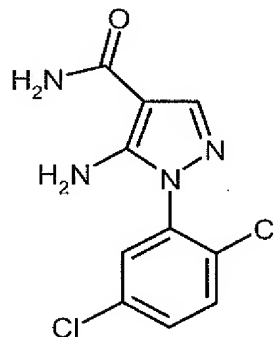
- 5 In analogy to the preparation of Example 15A, 1.6 g (74% of theory) of the desired product are obtained from 2 g (7.9 mmol) of 5-amino-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonitrile (Example 4A) in a mixture of 25 ml of ethanol, 10 ml of 30% strength hydrogen peroxide and 40 ml of 25% strength ammonia by crystallization from the reaction solution.

LC-MS (Method 2): $R_t = 2.5$ min.

MS (ESI pos): $m/z = 271$ ($M+H$)⁺.

10 **Example 19A**

5-Amino-1-(2,5-dichlorophenyl)-1H-pyrazole-4-carboxamide



In analogy to the preparation of Example 15A, 2.02 g (94% of theory) of the desired product are obtained from 2 g (7.9 mmol) of 5-amino-1-(2,5-dichlorophenyl)-1H-pyrazole-4-carbonitrile

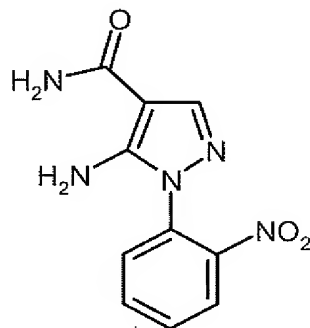
(Example 5A) in a mixture of 25 ml of ethanol, 18 ml of 30% strength hydrogen peroxide and 40 ml of 25% strength ammonia by crystallization from the reaction solution.

LC-MS (Method 2): $R_t = 2.8$ min.

MS (ESI pos): $m/z = 271$ ($M+H$)⁺.

5 **Example 20A**

5-Amino-1-(2-nitrophenyl)-1H-pyrazole-4-carboxamide



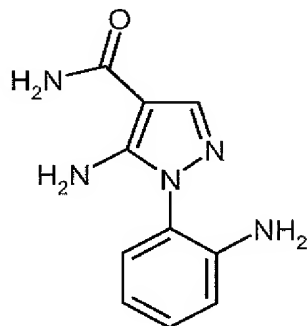
In analogy to the preparation of Example 15A, 1.4 g (86% of theory) of the desired product are obtained from 1.5 g (6.5 mmol) of 5-amino-1-(2-nitrophenyl)-1H-pyrazole-4-carbonitrile (Example 6A) in a mixture of 25 ml of ethanol, 16 ml of 30% strength hydrogen peroxide and 40 ml of 25% strength ammonia by crystallization from the reaction solution.

LC-MS (Method 2): $R_t = 2.3$ min.

MS (ESI pos): $m/z = 248$ ($M+H$)⁺.

Example 21A

5-Amino-1-(2-aminophenyl)-1H-pyrazole-4-carboxamide



1.28 g (5.27 mmol) of 5-amino-1-(2-nitrophenyl)-1H-pyrazole-4-carboxamide (Example 20A) are introduced into 30 ml of ethyl acetate and stirred with 5.8 g (25.8 mmol) of tin(II) chloride dihydrate at 70°C for 16 hours. After cooling to room temperature, the solution is adjusted to pH 9-10 with saturated sodium bicarbonate solution. The tin salts precipitated thereby are filtered off
5 through kieselguhr. The filtrate is extracted with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution. After drying over sodium sulphate, the solvent is removed in vacuo. 0.82 g (72% of theory) of the desired product is obtained.

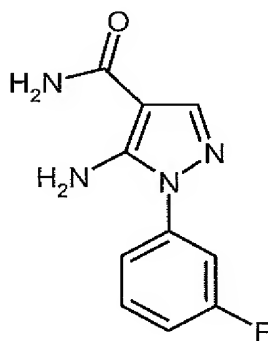
LC-MS (Method 4): $R_t = 3.0$ min.

MS (ESI pos): $m/z = 218$ ($M+H$)⁺

10 ¹H-NMR (300 MHz, DMSO-d₆): $\delta = 5.04$ (s, 2H), 6.00 (s, 2H), 6.66 (m, 1H), 6.89 (m, 1H), 7.03 (m, 2H), 7.92 (s, 1H) ppm.

Example 22A

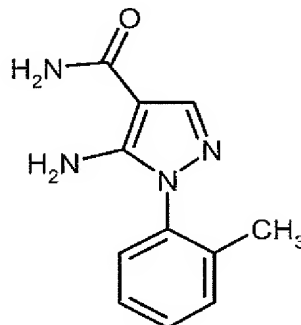
5-Amino-1-(3-fluorophenyl)-1H-pyrazole-4-carboxamide



15 In analogy to the preparation of Example 15A, 1.1 g (75% of theory) of the desired product are obtained from 1.3 g (6.4 mmol) of 5-amino-1-(3-fluorophenyl)-1H-pyrazole-4-carbonitrile (Example 7A) in a mixture of 25 ml of ethanol, 10 ml of 30% strength hydrogen peroxide and 40 ml of 25% strength ammonia by crystallization from the reaction solution.

LC-MS (Method 2): $R_t = 2.6$ min.

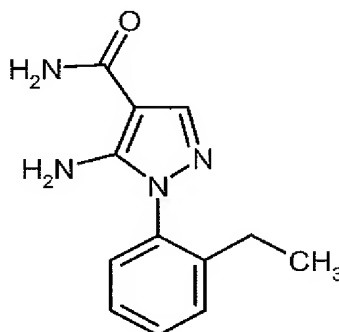
20 MS (ESI pos): $m/z = 221$ ($M+H$)⁺.

Example 23A**5-Amino-1-(2-methylphenyl)-1H-pyrazole-4-carboxamide**

300 ml of 96% strength sulphuric acid are cautiously added to 40.0 g (201.8 mmol) of 5-amino-1-(2-methylphenyl)-1H-pyrazole-4-carbonitrile (Example 8A) while cooling in ice. The mixture is
5 then heated to 40°C and stirred for 2 hours at this temperature. After cooling, it is poured into 2 l of ice-water and cautiously neutralized with 50% strength sodium hydroxide solution. After extraction with ethyl acetate three times (2 l each time) the combined organic phases are washed with saturated sodium chloride solution and dried over sodium sulphate, and the solvent is distilled off under reduced pressure. 36.0 g (82% of theory) of product (purity >90%) are obtained and are
10 employed without further purification in subsequent reactions.

LC-MS (Method 1): $R_t = 2.14$ min.

MS (ESI pos): $m/z = 217$ ($M+H$)⁺.

Example 24A**5-Amino-1-(2-ethylphenyl)-1H-pyrazole-4-carboxamide**

15

In analogy to the preparation of Example 15A, 2.58 g (87% of theory) of the desired product are obtained from 2.75 g (12.8 mmol) of 5-amino-1-(2-ethylphenyl)-1H-pyrazole-4-carbonitrile

(Example 9A) in a mixture of 106 ml of ethanol, 27 ml of 30% strength hydrogen peroxide and 133 ml of 25% strength ammonia after chromatography on silica gel (mobile phase dichloromethane with 0-10% methanol).

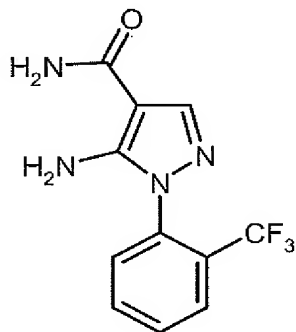
m.p.: 147°C

5 MS (ESI pos): $m/z = 231$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.0$ (t, 3H), 2.4 (q, 2H), 5.95 (s, 2H), 6.3 (broad d, 2H), 7.2-7.5 (m, 4H), 7.8 (s, 1H) ppm.

Example 25A

5-Amino-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carboxamide



10

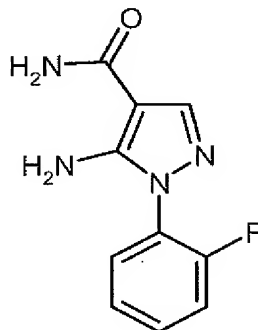
In analogy to the preparation of Example 15A, 4.01 g (87% of theory) of the desired product are obtained from 5.0 g (19.8 mmol) of 5-amino-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonitrile (Example 10A) in a mixture of 195 ml of ethanol, 49 ml of 30% strength hydrogen peroxide and 244 ml of 25% strength ammonia after chromatography on silica gel (mobile phase dichloromethane with 0-10% methanol).

15

m.p.: 186°C

MS (ESI pos): $m/z = 271$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 6.1$ (s, 2H), 7.0 (broad d, 2H), 7.45-8.0 (m, 5H) ppm.

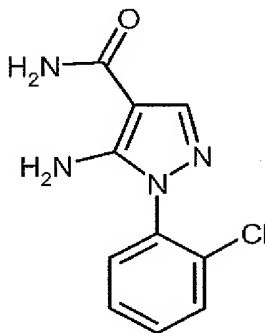
Example 26A**5-Amino-1-(2-fluorophenyl)-1H-pyrazole-4-carboxamide**

In analogy to the preparation of Example 15A, 3.89 g (81% of theory) of the desired product are
5 obtained from 5.0 g (21.9 mmol, 89% purity) of 5-amino-1-(2-fluorophenyl)-1H-pyrazole-4-carbonitrile (Example 11A) in a mixture of 173 ml of ethanol, 43 ml of 30% strength hydrogen peroxide and 216 ml of 25% strength ammonia after chromatography on silica gel (mobile phase dichloromethane with 0-10% methanol).

m.p.: 181°C

10 MS (ESI pos): $m/z = 221$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 6.2$ (s, 2H), 7.0 (broad d, 2H), 7.3-7.6 (m, 4H), 7.9 (s, 1H) ppm.

Example 27A**5-Amino-1-(2-chlorophenyl)-1H-pyrazole-4-carboxamide**

15

In analogy to the preparation of Example 15A, 3.93 g (79% of theory) of the desired product are obtained from 4.6 g (21.0 mmol) of 5-amino-1-(2-chlorophenyl)-1H-pyrazole-4-carbonitrile

(Example 12A) in a mixture of 159 ml of ethanol, 39 ml of 30% strength hydrogen peroxide and 198 ml of 25% strength ammonia after chromatography on silica gel (mobile phase dichloromethane with 0-10% methanol).

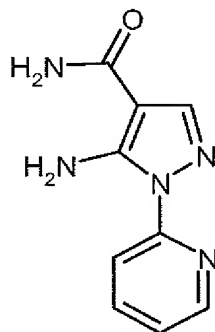
m.p.: 166°C

5 MS (ESI pos): $m/z = 237 (M+H)^+$

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): $\delta = 6.1$ (s, 2H), 7.0 (broad d, 2H), 7.4-7.7 (m, 4H), 7.85 (s, 1H) ppm.

Example 28A

5-Amino-1-(2-pyridinyl)-1H-pyrazole-4-carboxamide



10

In analogy to the preparation of Example 15A, 2.28 g (90% of theory) of the desired product are obtained from 2.3 g (12.4 mmol) of 5-amino-1-(2-pyridinyl)-1H-pyrazole-4-carbonitrile (Example 13A) in a mixture of 90 ml of ethanol, 23 ml of 30% strength hydrogen peroxide and 113 ml of 25% strength ammonia after chromatography on silica gel (mobile phase dichloromethane with 0-10% methanol).

15

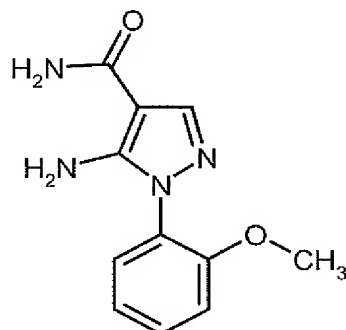
m.p.: 218°C

MS (DCI): $m/z = 204 (M+H)^+$

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): $\delta = 7.1$ (broad d, 2H), 7.3 (dd, 1H), 7.5 (s, 2H), 7.85 (d, 1H), 7.95 (s, 1H), 8.0 (dd, 1H), 8.45 (d, 1H) ppm.

Example 29A

5-Amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxamide



In analogy to the preparation of Example 15A, 2.61 g (70% of theory) of the desired product are
5 obtained from 3.5 g (16.0 mmol, 98% purity) of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carbonitrile (Example 14A) in a mixture of 172 ml of ethanol, 34 ml of 30% strength hydrogen peroxide and 137 ml of 25% strength ammonia after chromatography on silica gel (mobile phase dichloromethane with 0-10% methanol).

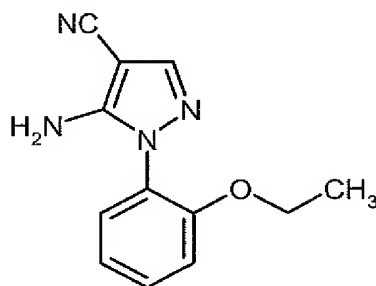
m.p.: 191°C

10 MS (ESI pos): $m/z = 233$ (M+H)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 3.8$ (s, 3H), 5.9 (s, 2H), 7.0 (broad s, 2H), 7.05-7.55 (m, 4H), 7.8 (s, 1H) ppm.

Example 30A

5-Amino-1-(2-ethoxyphenyl)-1H-pyrazole-4-carbonitrile



15

In analogy to the preparation of Example 1A, 2.9 g (59% of theory) of the desired product are obtained starting from 4.0 g (21.2 mmol) of 2-ethoxyphenylhydrazine hydrochloride, 2.5 g (21.2 mmol) of ethoxymethylenemalononitrile and 8.8 ml (63.6 mmol) of triethylamine.

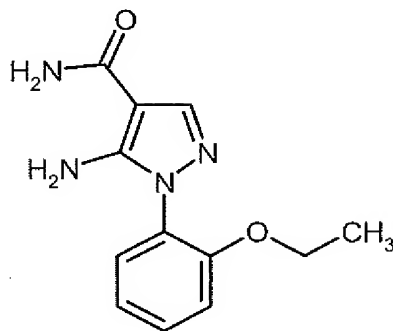
LC-MS (Method 1): $R_t = 2.32$ min.

MS (ESI pos): $m/z = 229$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO- d_6): $\delta = 1.25$ (t, 3H), 4.08 (q, 2H), 6.37 (s, 2H), 7.04 (m, 1H), 7.25 (m, 2H), 7.45 (m, 1H), 7.71 (s, 1H) ppm.

5 Example 31A

5-Amino-1-(2-ethoxyphenyl)-1H-pyrazole-4-carboxamide



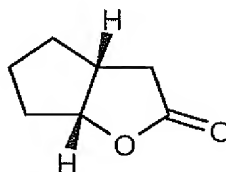
In analogy to the preparation of Example 15A, 2.2 g (84% of theory) of the desired product are obtained from 2.5 g (10.9 mmol) of 5-amino-1-(2-ethoxyphenyl)-1H-pyrazole-4-carbonitrile (Example 30A) in a mixture of 20 ml of ethanol, 10 ml of 30% strength hydrogen peroxide and 10 ml of 25% strength ammonia.

LC-MS (Method 4): $R_t = 1.73$ min.

MS (ESI pos): $m/z = 247$ ($M+H$)⁺.

Example 32A

15 *cis*-Hexahydro-2*H*-cyclopenta[*b*]furan-2-one



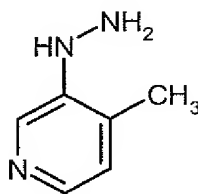
32 ml of concentrated sulphuric acid (96% strength) are cooled to -10°C . Then 5.0 g (39.6 mmol) of 2-cyclopenten-1-ylacetic acid are slowly metered in, and the reaction mixture is stirred at the same temperature for 1 h. It is poured into 100 ml of ice-water and extracted with 100 ml of diethyl

ether. The organic phase is dried over sodium sulphate and the solvent is cautiously distilled off. 2.9 g of the racemic lactone are obtained in 70% purity (LC-MS) and are employed further as crude product.

MS (ESI pos): $m/z = 127$ ($M+H$)⁺.

5 **Example 33A**

3-Hydrazino-4-methylpyridine



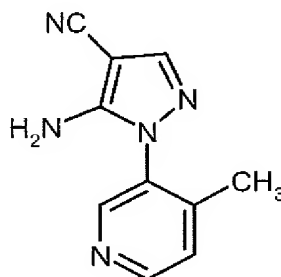
2.55 ml of a 2.5 M aqueous sodium nitrite solution are added to a solution of 4.0 g (37 mmol) of 3-amino-4-methylpyridine in 19 ml of 6 N hydrochloric acid while cooling in an ice/salt bath. The
10 resulting diazonium salt solution is slowly added dropwise at -10°C to -15°C to a solution of 21 g (111 mmol) of tin(II) chloride in 26 ml of hydrochloric acid. The solution is left to stand in a refrigerator overnight in order to complete the reaction. The precipitated solid is filtered off with suction, suspended in 26 ml of water, made basic with concentrated sodium hydroxide solution and filtered. The filtrate is extracted ten times with 20 ml of dichloromethane each time, and the
15 combined organic phases are dried over sodium sulphate and concentrated. Drying under high vacuum results in 1.45 g (31% of theory) of the desired product as a colourless oil.

MS (ESI pos): $m/z = 124$ ($M+H$)⁺

¹H-NMR (400 MHz, DMSO-d₆): $\delta = 2.05$ (s, 3H), 4.05 (s, 2H), 6.4 (s, 1H), 6.9 (d, 1H), 7.75 (d, 1H), 8.3 (s, 1H) ppm.

Example 34A

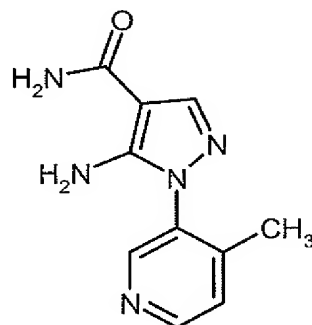
5-Amino-1-(4-methylpyridin-3-yl)-1H-pyrazole-4-carbonitrile



5 In analogy to the preparation of Example 1A, 1.75 g (75% of theory) of the desired product are obtained starting from 1.44 g (11.7 mmol) of 3-hydrazino-4-methylpyridine (Example 33A), 1.47 g (11.7 mmol) of ethoxymethylenemalononitrile and 4.9 ml (35 mmol) of triethylamine.

MS (ESI pos): $m/z = 200$ (M+H)⁺¹H-NMR (300 MHz, DMSO-d₆): $\delta = 2.1$ (s, 3H), 6.7 (s, 2H), 7.45 (d, 1H), 7.8 (s, 1H), 8.4 (s, 1H), 8.55 (d, 1H) ppm.10 **Example 35A**

5-Amino-1-(4-methylpyridin-3-yl)-1H-pyrazole-4-carboxamide



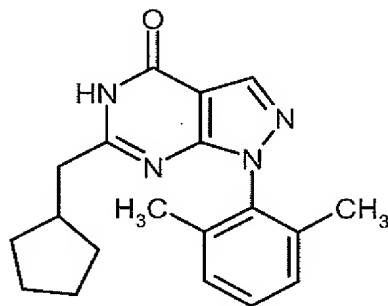
15 In analogy to the preparation of Example 15A, 1.75 g (91% of theory) of the desired product are obtained from 1.75 g (8.78 mmol) of 5-amino-1-(4-methylpyridin-3-yl)-1H-pyrazole-4-carbonitrile (Example 34A) in a mixture of 105 ml of ethanol, 9.2 ml of 30% strength hydrogen peroxide and 84 ml of 25% strength ammonia.

MS (ESI pos): $m/z = 218$ (M+H)⁺

¹H-NMR (200 MHz, DMSO-d₆): δ = 2.1 (s, 3H), 6.2 (s, 2H), 6.6-7.5 (2 broad s, 2H), 7.45 (d, 1H), 7.9 (s, 1H), 8.4 (s, 1H), 8.5 (d, 1H) ppm.

Exemplary embodiments:**Example 1**

6-Cyclopentylmethyl-1-(2,6-dimethylphenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one



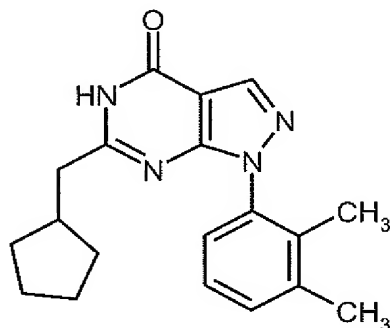
- 5 0.1 g (0.43 mmol) of 5-amino-1-(2,6-dimethylphenyl)-1H-pyrazole-4-carboxamide (Example 15A) is dissolved under argon in 6 ml of absolute ethanol and 0.24 g (1.7 mmol) of methyl cyclopentylacetate and 0.17 g (4.34 mmol) of 60% sodium hydride (suspension in mineral oil) are added. The reaction mixture is heated to reflux overnight. Cooling to room temperature is followed by acidification with concentrated hydrochloric acid. The sodium chloride precipitated thereby is
- 10 filtered off. The filtrate is concentrated in vacuo, and the remaining residue is purified by preparative HPLC (YMC Gel ODS-AQ S 5/15 μ m; eluent A: water, eluent B: acetonitrile; gradient: 0 min 30% B, 5 min 30% B, 50 min 95% B). 74 mg (53% of theory) of the product are obtained as a colourless solid.

LC-MS (Method 3): $R_t = 3.79$ min.

- 15 MS (ESI pos): $m/z = 323$ ($M+H$)⁺.

Example 2

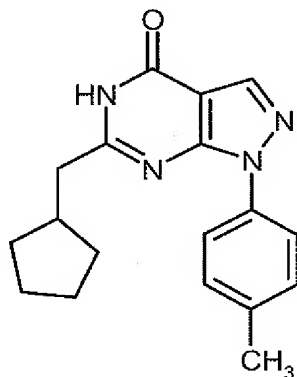
6-Cyclopentylmethyl-1-(2,3-dimethylphenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one



- 0.1 g (0.43 mmol) of 5-amino-1-(2,3-dimethylphenyl)-1H-pyrazole-4-carboxamide (Example 16A) is dissolved under argon in 6 ml of absolute ethanol and 0.24 g (1.7 mmol) of methyl cyclopentylacetate and 0.17 g (4.34 mmol) of 60% sodium hydride (suspension in mineral oil) are added. The reaction mixture is heated to reflux overnight. Cooling to room temperature is followed by acidification with concentrated hydrochloric acid. The mixture of sodium chloride and the product precipitated thereby is filtered off and washed several times with water and diethyl ether.
- Drying under high vacuum results in 69 mg (49% of theory) of the product as colourless solid.

LC-MS (Method 3): $R_t = 3.57$ min.MS (ESI pos): $m/z = 323$ ($M+H$)⁺

- ¹H-NMR (300 MHz, DMSO- d_6): $\delta = 1.17$ (m, 2H), 1.48 (m, 2H), 1.59 (m, 4H), 1.87 (s, 3H), 2.19 (m, 1H), 2.33 (s, 3H), 2.54 (d, 2H), 7.16 (d, 1H), 7.25 (t, 1H), 7.36 (d, 1H), 8.21 (s, 1H), 12.12 (s, 1H) ppm.

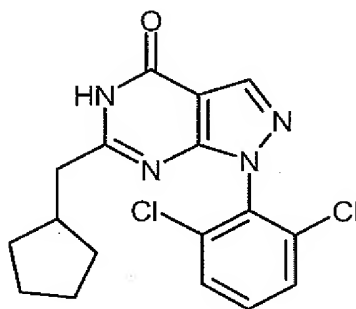
Example 3**6-Cyclopentylmethyl-1-(4-methylphenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one**

- In analogy to the preparation of Example 1, 97 mg (68% of theory) of the desired product are obtained as a colourless solid starting from 0.88 g (0.41 mmol) of 5-amino-1-(4-methylphenyl)-1H-pyrazole-4-carboxamide (Example 17A), 0.26 g (1.8 mmol) of methyl cyclopentylacetate and 0.16 g (4.09 mmol) of 60% sodium hydride.

LC-MS (Method 3): $R_t = 4.09$ min.

MS (ESI pos): $m/z = 309$ ($M+H$)⁺

- ¹H-NMR (300 MHz, DMSO- d_6): $\delta = 1.23$ (m, 2H), 1.57 (m, 2H), 1.72 (m, 4H), 2.34 (m, 1H), 2.36 (s, 3H), 2.66 (d, 2H), 7.34 (d, 1H), 7.92 (d, 1H), 8.23 (s, 1H), 12.27 (s, 1H) ppm.

Example 4**6-Cyclopentylmethyl-1-(2,6-dichlorophenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one**

- In analogy to the preparation of Example 2, 61 mg (45% of theory) of the desired product are obtained as a colourless solid starting from 0.1 g (0.37 mmol) of 5-amino-1-(2,6-dichlorophenyl)-

1H-pyrazole-4-carboxamide (Example 18A), 0.2 g (1.4 mmol) of methyl cyclopentylacetate and 0.14 g (3.6 mmol) of 60% sodium hydride.

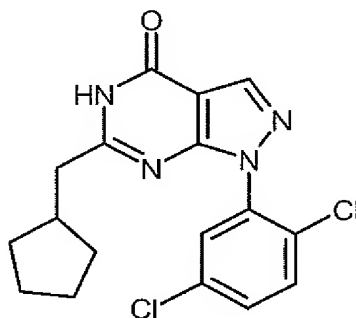
LC-MS (Method 3): $R_t = 3.73$ min.

MS (ESI pos): $m/z = 363$ (M+H)⁺

- 5 ¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.15$ (m, 2H), 1.49 (m, 2H), 1.60 (m, 4H), 2.21 (m, 1H), 2.57 (d, 2H), 7.60 (m, 2H), 7.69 (m, 1H), 8.41 (s, 1H), 12.51 (s, 1H) ppm.

Example 5

6-Cyclopentylmethyl-1-(2,5-dichlorophenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one



- 10 In analogy to the preparation of Example 1, 32 mg (23% of theory) of the desired product are obtained as a colourless solid starting from 0.1 g (0.37 mmol) of 5-amino-1-(2,5-dichlorophenyl)-1H-pyrazole-4-carboxamide (Example 19A), 0.2 g (1.4 mmol) of methyl cyclopentylacetate and 0.14 g (3.6 mmol) of 60% sodium hydride.

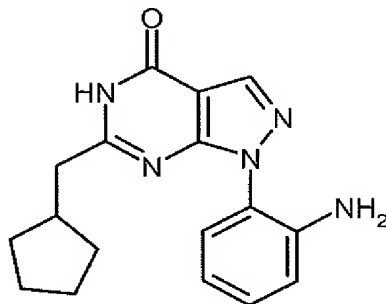
LC-MS (Method 3): $R_t = 4.0$ min.

- 15 MS (ESI pos): $m/z = 363$ (M+H)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.15$ (m, 2H), 1.49 (m, 2H), 1.60 (m, 4H), 2.22 (m, 1H), 2.55 (d, 2H), 7.16 (d, 1H), 7.31 (m, 1H), 7.32 (m, 2H), 8.23 (s, 1H), 12.39 (s, 1H) ppm.

Example 6

1-(2-Aminophenyl)-6-cyclopentylmethyl-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one



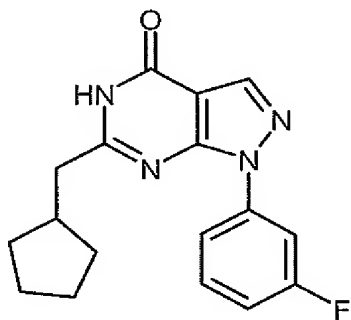
- In analogy to the preparation of Example 1, 61 mg (42% of theory) of the desired product are obtained as a colourless solid starting from 0.1 g (0.46 mmol) of 5-amino-1-(2-aminophenyl)-1H-pyrazole-4-carboxamide (Example 21A), 0.19 g (1.4 mmol) of methyl cyclopentylacetate and 0.18 g (4.6 mmol) of 60% sodium hydride.

LC-MS (Method 4): $R_t = 3.9$ min.MS (ESI pos): $m/z = 310$ ($M+H$)⁺

- ¹H-NMR (300 MHz, DMSO- d_6): $\delta = 1.17$ (m, 2H), 1.45 (m, 2H), 1.56 (m, 4H), 2.19 (m, 1H), 2.52 (d, 2H), 6.12 (s, 2H), 6.64 (m, 1H), 6.90 (m, 1H), 7.05 (m, 2H), 8.25 (s, 1H), 12.47 (s, 1H) ppm.

Example 7

6-Cyclopentylmethyl-1-(3-fluorophenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one



- In analogy to the preparation of Example 1, 82 mg (58% of theory) of the desired product are obtained as a colourless solid starting from 0.1 g (0.45 mmol) of 5-amino-1-(3-fluorophenyl)-1H-pyrazole-4-carboxamide (Example 22A), 0.26 g (1.8 mmol) of methyl cyclopentylacetate and 0.18 g (4.5 mmol) of 60% sodium hydride.

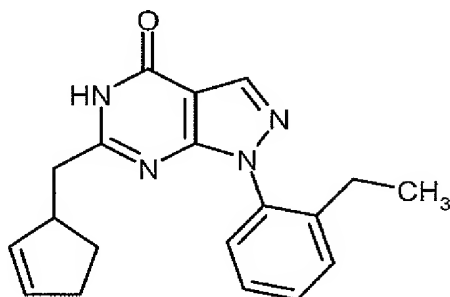
LC-MS (Method 3): $R_t = 3.74$ min.

MS (ESI pos): $m/z = 313$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO- d_6): $\delta = 1.12$ (m, 2H), 1.58 (m, 2H), 1.75 (m, 4H), 2.34 (m, 1H), 2.69 (d, 2H), 7.23 (m, 1H), 7.63 (m, 1H), 8.00 (m, 2H), 8.31 (s, 1H), 12.37 (s, 1H) ppm.

5 **Example 8**

6-(2-Cyclopenten-1-ylmethyl)-1-(2-ethylphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



In analogy to the preparation of Example 1, 64 mg (31% of theory) of the desired product are obtained as a colourless solid starting from 0.15 g (0.65 mmol) of 5-amino-1-(2-ethylphenyl)-1H-pyrazole-4-carboxamide (Example 24A), 0.27 g (1.95 mmol) of methyl 2-cyclopenten-1-ylacetate and 0.13 g (3.2 mmol) of 60% sodium hydride.

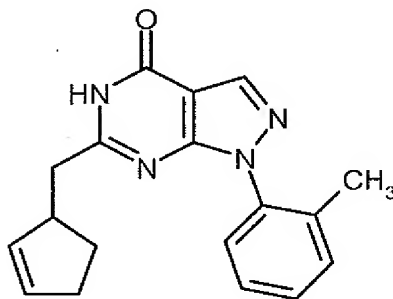
m.p.: 146°C

MS (ESI pos): $m/z = 321$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO- d_6): $\delta = 0.95$ (t, 3H), 1.45 (m, 1H), 1.95 (m, 1H), 2.1-2.75 (m, 6H), 3.0 (m, 1H), 5.5-5.8 (m, 2H), 7.25-7.5 (m, 4H), 8.2 (s, 1H), 12.2 (s, 1H) ppm.

Example 9

6-(2-Cyclopenten-1-ylmethyl)-1-(2-methylphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



In analogy to the preparation of Example 1, 44 mg (26% of theory) of the desired product are
5 obtained as a colourless solid starting from 0.12 g (0.56 mmol) of 5-amino-1-(2-methylphenyl)-1H-
pyrazole-4-carboxamide (Example 23A), 0.24 g (1.7 mmol) of methyl 2-cyclopenten-1-ylacetate
and 0.11 g (2.8 mmol) of 60% sodium hydride.

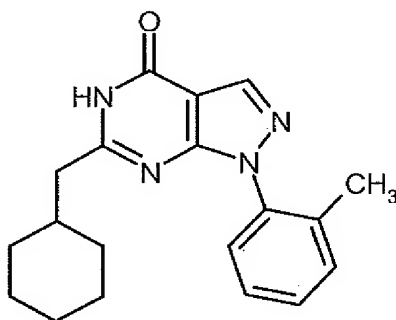
m.p.: 179°C

MS (ESI pos): $m/z = 307$ (M+H)⁺

10 ¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.45$ (m, 1H), 1.95 (m, 1H), 2.1 (s, 3H), 2.1-2.75 (m, 4H),
3.05 (m, 1H), 5.5-5.8 (m, 2H), 7.3-7.5 (m, 4H), 8.25 (s, 1H), 12.2 (s, 1H) ppm.

Example 10

6-Cyclohexylmethyl-1-(2-methylphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



15 In analogy to the preparation of Example 1, 65 mg (29% of theory) of the desired product are
obtained as a colourless solid starting from 0.15 g (0.68 mmol) of 5-amino-1-(2-methylphenyl)-1H-
pyrazole-4-carboxamide (Example 23A), 0.35 g (2.04 mmol) of ethyl cyclohexylacetate and
0.136 g (3.4 mmol) of 60% sodium hydride.

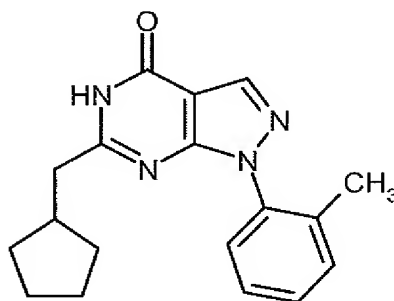
m.p.: 169°C

MS (ESI pos): $m/z = 323$ (M+H)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 0.9-1.3$ (m, 5H), 1.5-1.9 (m, 6H), 2.1 (s, 3H), 2.45 (d, 2H), 7.3-7.5 (m, 4H), 8.2 (s, 1H), 12.2 (s, 1H) ppm.

5 **Example 11**

6-Cyclopentylmethyl-1-(2-methylphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



In analogy to the preparation of Example 1, 43 mg (30% of theory) of the desired product are obtained as a colourless solid starting from 0.1 g (0.46 mmol) of 5-amino-1-(2-methylphenyl)-1H-pyrazole-4-carboxamide (Example 23A), 0.237 g (92% purity, 1.39 mmol) of ethyl
10 cyclopentylacetate and 0.093 g (2.32 mmol) of 60% sodium hydride.

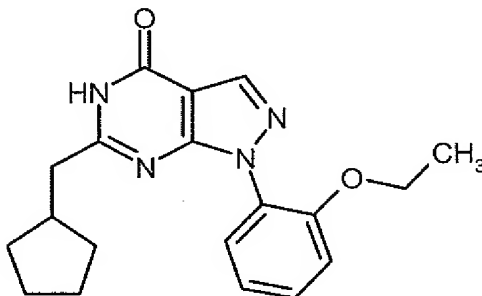
m.p.: 181°C

MS (ESI pos): $m/z = 309$ (M+H)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.1-1.55$ (m, 8H), 2.1 (s, 3H), 2.2 (m, 1H), 2.55 (d, 2H), 7.3-
15 7.5 (m, 4H), 8.2 (s, 1H), 12.15 (s, 1H) ppm.

Example 12

6-Cyclopentylmethyl-1-(2-ethoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



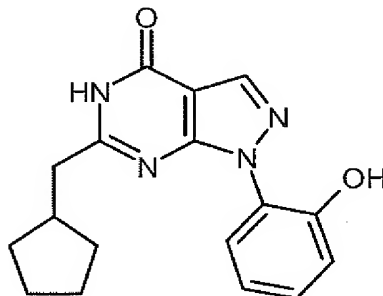
In analogy to the preparation of Example 1, 73 mg (52% of theory) of the desired product were
5 obtained as a colourless solid starting from 0.1 g (0.41 mmol) of 5-amino-1-(2-ethoxyphenyl)-1H-pyrazole-4-carboxamide (Example 31A), 0.231 g (1.6 mmol) of ethyl cyclopentylacetate and 0.162 g (4.1 mmol) of 60% sodium hydride.

LC-MS (Method 3): $R_t = 3.5$ min.MS (ESI pos): $m/z = 339$ ($M+H$)⁺

10 ¹H-NMR (300 MHz, DMSO- d_6): $\delta = 1.10$ (t, 3H), 1.22 (m, 2H), 1.45 (m, 2H), 1.59 (m, 4H), 1.96 (m, 1H), 2.54 (d, 2H), 4.02 (q, 2H), 7.08 (m, 1H), 7.23 (m, 1H), 7.37 (m, 1H), 7.48 (m, 1H), 8.16 (s, 1H), 12.06 (s, 1H) ppm.

Example 13

6-Cyclopentylmethyl-1-(2-hydroxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



15

4 ml of 1 M boron tribromide solution in dichloromethane are added to 0.2 g (0.59 mmol) of 6-cyclopentylmethyl-1-(2-ethoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Example 12), and the reaction mixture was stirred at room temperature for 1 h. Aqueous hydrolysis is followed by extraction with dichloromethane. The product is purified by preparative

HPLC (YMC Gel ODS-AQ S 5/15 μm ; eluent A: water, eluent B: acetonitrile; gradient: 0 min 30% B, 5 min 30% B, 50 min 95% B). 0.167 g (91% of theory) of the product is obtained as a colourless solid.

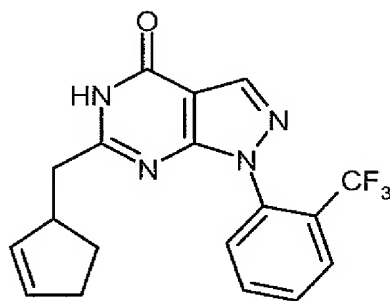
LC-MS (Method 4): $R_t = 2.54$ min.

5 MS (ESI pos): $m/z = 311$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO- d_6): $\delta = 1.17$ (m, 2H), 1.42 (m, 6H), 2.19 (m, 1H), 2.54 (d, 2H), 6.93 (m, 1H), 7.04 (m, 1H), 7.32 (m, 1H), 8.18 (s, 1H), 9.92 (s, 1H), 12.12 (s, 1H) ppm.

Example 14

6-(2-Cyclopenten-1-ylmethyl)-1-[2-(trifluoromethyl)phenyl]-1,5-dihydro-4H-pyrazolo[3,4-
10 d]pyrimidin-4-one



In analogy to the preparation of Example 1, 57 mg (29% of theory) of the desired product are obtained as a colourless solid starting from 0.15 g (0.56 mmol) of 5-amino-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxamide (Example 25A), 0.233 g (1.67 mmol) of
15 methyl 2-cyclopenten-1-ylacetate and 0.111 g (2.78 mmol) of 60% sodium hydride.

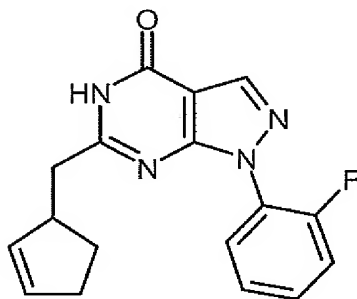
m.p.: 153°C

MS (ESI pos): $m/z = 361$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO- d_6): $\delta = 1.45$ (m, 1H), 1.9 (m, 1H), 2.1-2.4 (m, 2H), 2.45-2.7 (m, 2H), 3.0 (m, 1H), 5.5-5.8 (m, 2H), 7.6 (d, 1H), 7.75-8.0 (m, 3H), 8.25 (s, 1H), 12.2 (s, 1H) ppm.

Example 15

6-(2-Cyclopenten-1-ylmethyl)-1-(2-fluorophenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



In analogy to the preparation of Example 1, 77 mg (37% of theory) of the desired product are
5 obtained as a colourless solid starting from 0.15 g (0.66 mmol) of 5-amino-1-(2-fluorophenyl)-1H-
pyrazole-4-carboxamide (Example 26A), 0.279 g (1.99 mmol) of methyl 2-cyclopenten-1-ylacetate
and 0.133 g (2.78 mmol) of 60% sodium hydride.

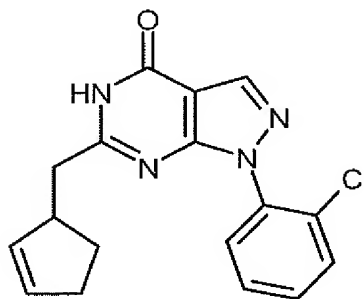
m.p.: 163°C

MS (ESI pos): $m/z = 311$ ($M+H$)⁺

10 ¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.5$ (m, 1H), 1.95 (m, 1H), 2.1-2.45 (m, 2H), 2.45-2.7 (m,
2H), 3.0 (m, 1H), 5.6-5.8 (m, 2H), 7.3-7.7 (m, 4H), 8.3 (s, 1H), 12.3 (s, 1H) ppm.

Example 16

6-(2-Cyclopenten-1-ylmethyl)-1-(2-chlorophenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



15 In analogy to the preparation of Example 1, 50 mg (24% of theory) of the desired product are
obtained as a colourless solid starting from 0.15 g (0.63 mmol) of 5-amino-1-(2-chlorophenyl)-1H-
pyrazole-4-carboxamide (Example 27A), 0.266 g (1.90 mmol) of methyl 2-cyclopenten-1-ylacetate
and 0.127 g (3.17 mmol) of 60% sodium hydride.

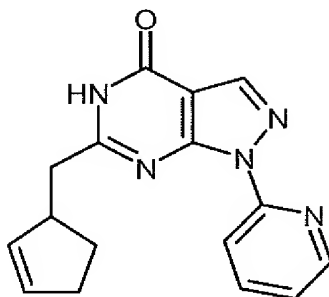
m.p.: 150°C

MS (ESI pos): $m/z = 327 (M+H)^+$

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): $\delta = 1.5$ (m, 1H), 1.95 (m, 1H), 2.1-2.4 (m, 2H), 2.5-2.7 (m, 2H), 3.05 (m, 1H), 5.6-5.8 (m, 2H), 7.5-7.8 (m, 4H), 8.25 (s, 1H), 12.2 (s, 1H) ppm.

5 **Example 17**

6-(2-Cyclopenten-1-ylmethyl)-1-(2-pyridinyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



In analogy to the preparation of Example 1, 76 mg (35% of theory) of the desired product are obtained as a colourless solid starting from 0.15 g (0.74 mmol) of 5-amino-1-(2-pyridinyl)-1H-pyrazole-4-carboxamide (Example 28A), 0.31 g (2.21 mmol) of methyl 2-cyclopenten-1-ylacetate and 0.147 g (3.69 mmol) of 60% sodium hydride.

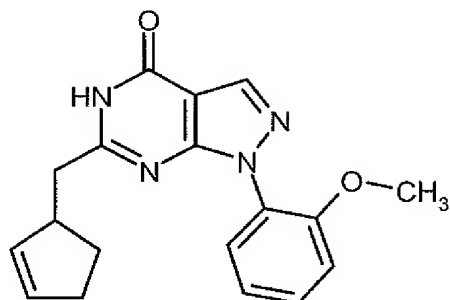
m.p.: 239°C

MS (ESI pos): $m/z = 294 (M+H)^+$

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): $\delta = 1.55$ (m, 1H), 2.0 (m, 1H), 2.15-2.45 (m, 2H), 2.55-2.75 (m, 2H), 3.15 (m, 1H), 5.65-5.8 (m, 2H), 7.5 (dd, 1H), 8.0 (d, 1H), 8.05 (m, 1H), 8.3 (s, 1H), 8.6 (d, 1H), 12.3 (s, 1H) ppm.

Example 18

6-(2-Cyclopenten-1-ylmethyl)-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



In analogy to the preparation of Example 1, 82 mg (39% of theory) of the desired product are obtained as a colourless solid starting from 0.15 g (0.65 mmol) of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxamide (Example 29A), 0.272 g (1.94 mmol) of methyl 2-cyclopenten-1-ylacetate and 0.129 g (3.23 mmol) of 60% sodium hydride.

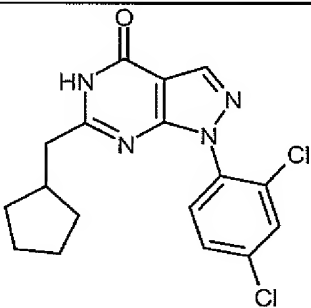
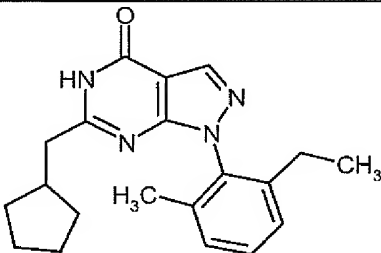
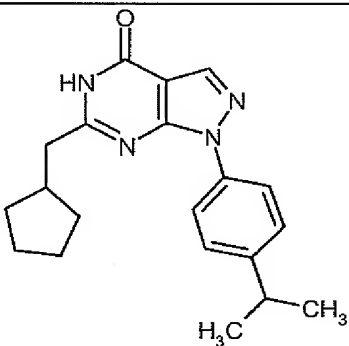
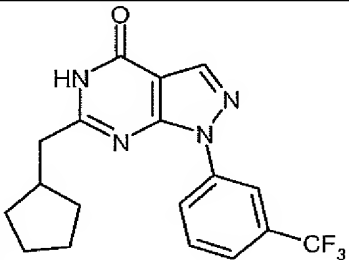
m.p.: 182°C

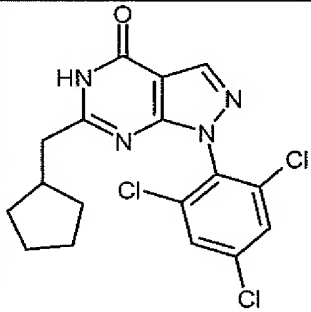
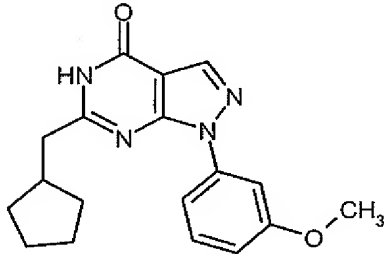
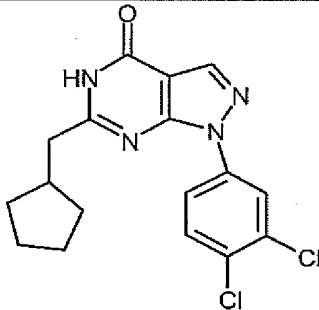
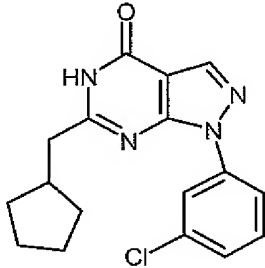
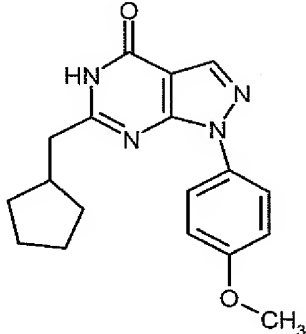
MS (ESI pos): $m/z = 323$ ($M+H$)⁺

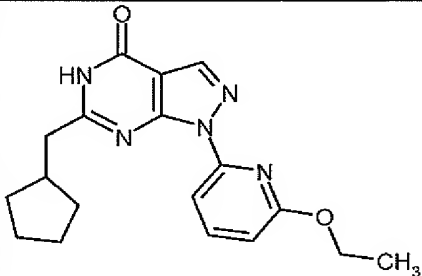
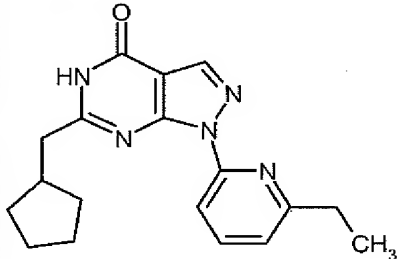
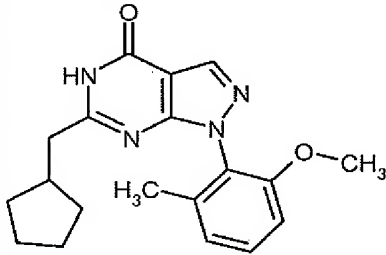
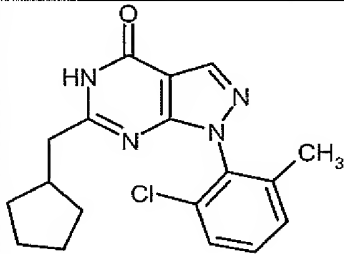
¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.5$ (m, 1H), 1.95 (m, 1H), 2.1-2.45 (m, 2H), 2.45-2.75 (m, 2H), 3.05 (m, 1H), 3.0 (s, 3H), 5.6-5.8 (m, 2H), 7.0-7.55 (m, 4H), 8.2 (s, 1H), 12.15 (s, 1H) ppm.

10 Exemplary embodiments 19 – 31 listed in Table 2 below are obtained just like the corresponding starting compounds in analogy to the examples described above:

Table 2:

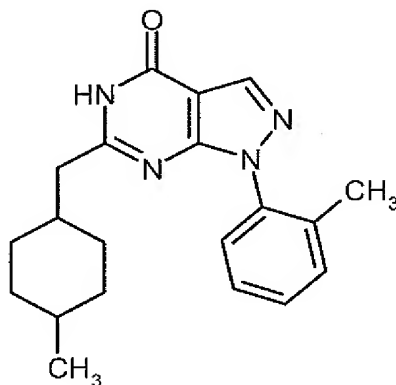
| Ex. No. | Structure | Yield [% of th.] | MS: m/z [M+H] ⁺ | R _t [min] | LC-MS method |
|---------|-------------------------------------------------------------------------------------|------------------|----------------------------|----------------------|--------------|
| 19 |  | 14.1 | 364 | 4.05 | 3 |
| 20 |  | 29.8 | 337 | 3.97 | 3 |
| 21 |  | 26.1 | 337 | 4.52 | 3 |
| 22 |  | 48.5 | 363 | 4.39 | 3 |

| Ex. No. | Structure | Yield [% of th.] | MS: m/z [M+H] ⁺ | R _t [min] | LC-MS method |
|---------|-------------------------------------------------------------------------------------|------------------|----------------------------|----------------------|--------------|
| 23 |  | 14.6 | 398 | 4.20 | 3 |
| 24 |  | 78.7 | 325 | 3.88 | 3 |
| 25 |  | 28.4 | 364 | 4.70 | 3 |
| 26 |  | 48.9 | 329 | 4.30 | 3 |
| 27 |  | 60.1 | 325 | 3.79 | 3 |

| Ex. No. | Structure | Yield [% of th.] | MS: m/z [M+H] ⁺ | R _t [min] | LC-MS method |
|---------|-------------------------------------------------------------------------------------|------------------|----------------------------|----------------------|--------------|
| 28 |  | 10.5 | 340 | 3.61 | 1 |
| 29 |  | 7.9 | 324 | 4.00 | 4 |
| 30 |  | 48.8 | 339 | 4.10 | 4 |
| 31 |  | 38.8 | 343 | 3.07 | 1 |

Example 32

6-[(4-Methylcyclohexyl)methyl]-1-(2-methylphenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one



150 mg (0.69 mmol) of 5-amino-1-(2-methylphenyl)-1H-pyrazole-4-carboxamide (Example 23A) and 130 mg (0.83 mmol) of 2-(4-methylcyclohexyl)acetic acid are mixed with 3 ml of trimethylsilyl polyphosphate and stirred at 130°C for 3 h. The hot reaction mixture is added to 20 ml of water and then extracted with dichloromethane (2 x 20 ml). The combined organic phases are washed with water (20 ml) and with saturated sodium chloride solution (20 ml) and dried over sodium sulphate. The solvent is distilled off under reduced pressure, and the crude product is purified by preparative HPLC (YMC Gel ODS-AQ S 5/15 µm; eluent A: water, eluent B: acetonitrile; gradient: 0 min 30% B, 5 min 30% B, 50 min 95% B). 182 g (78% of theory) of the product are obtained.

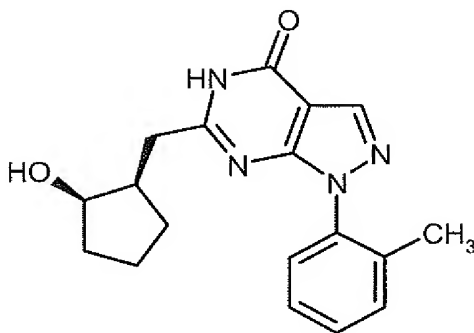
LC-MS (Method 3): $R_t = 4.09$ min.

MS (ESI pos): $m/z = 337$ ($M+H$)⁺

¹H-NMR (200 MHz, DMSO- d_6): $\delta = 0.68-0.90$ (5H), 0.99-1.61 (8H), 1.98-2.07 (4H), 2.16 (d, 1H), 7.19 (d, 1H), 7.28-7.51 (m, 3H), 8.26 (s, 1H), 10.27 (s, 1H) ppm.

Example 33

6-[(1,2-*cis*)-2-Hydroxycyclopentyl]methyl}-1-(2-methylphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (*racemate*)



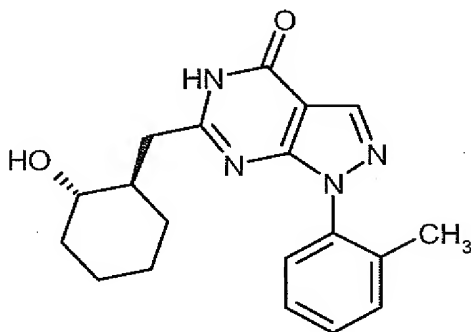
200 mg (0.93 mmol) of 5-amino-1-(2-methylphenyl)-1H-pyrazole-4-carboxamide (Example 23A) and 525 mg of *cis*-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (approx. 70% pure, Example 32A) are dissolved in 10 ml of absolute ethanol under argon, and 315 mg (4.6 mmol) of sodium ethoxide are added. The reaction mixture is heated to reflux overnight. Cooling to room temperature is followed by hydrolysis with 25 ml of water and then extraction with ethyl acetate (2 x 25 ml). The combined organic phases are dried over sodium sulphate, and the solvent is distilled off under reduced pressure. The crude product is purified by preparative HPLC (YMC Gel ODS-AQ S 5/15 μ m; eluent A: water, eluent B: acetonitrile; gradient: 0 min 30% B, 5 min 30% B, 50 min 95% B). 90 mg (30% of theory) of the desired product are obtained.

MS (ESI pos): $m/z = 325$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-*d*₆): $\delta = 1.28$ - 1.74 (7H), 2.07 (s, 3H), 2.55 (dd, 1H), 2.80 (dd, 1H), 3.97 (m, 1H), 4.43 (d, 1H), 7.36 (m, 2H), 7.43 (m, 2H), 8.22 (s, 1H), 12.07 (s, 1H) ppm.

Example 34

6-{[(1,2-*trans*)-2-Hydroxycyclohexyl]methyl}-1-(2-methylphenyl)-1,5-dihydro-4H-pyrazolo[3,4-*d*]pyrimidin-4-one



200 mg (0.93 mmol) of 5-amino-1-(2-methylphenyl)-1H-pyrazole-4-carboxamide (Example 23A) and 583 mg (4.16 mmol) of *rac*-hexahydro-1-benzofuran-2(3H)one (mixture of the *cis* and *trans*

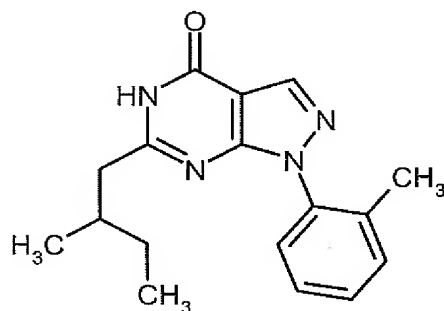
diastereomers; for preparation, see, for example, K.F. Podraza et al., *J. Heterocycl. Chem.* 1987, 24, 293-295) are dissolved in 10 ml of absolute ethanol under argon, and 315 mg (4.6 mmol) of sodium ethoxide are added. The reaction mixture is heated to reflux overnight. Cooling to room temperature is followed by hydrolysis with 25 ml of water and then extraction with ethyl acetate (2 x 25 ml). The combined organic phases are dried over sodium sulphate, and the solvent is distilled off under reduced pressure. The crude product is purified by preparative HPLC (YMC Gel ODS-AQ S 5/15 μ m; eluent A: water, eluent B: acetonitrile; gradient: 0 min 30% B, 5 min 30% B, 50 min 95% B). 68 mg (21% of theory) of the desired product are obtained.

MS (ESI pos): $m/z = 339$ ($M+H$)⁺

¹H-NMR (400 MHz, DMSO- d_6): $\delta = 0.97$ (m, 2H), 1.15 (m, 2H), 2.51 (d, 2H), 1.64 (m, 2H), 1.81 (m, 1H), 2.07 (s, 3H), 2.26 (dd, 1H), 2.99-3.10 (2H), 4.61 (d, 1H), 7.37 (m, 2H), 7.44 (m, 2H), 8.23 (s, 1H), 12.11 (s, 1H) ppm.

Example 35

6-(2-Methylbutyl)-1-(2-methylphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (*racemate*)



15

In analogy to the preparation of Example 1, 784 mg (71% of theory) of the desired product are obtained as a colourless solid starting from 0.8 g (3.7 mmol) of 5-amino-1-(2-methylphenyl)-1H-pyrazole-4-carboxamide (Example 23A), 2.72 g (98% purity, 18.5 mmol) of ethyl 3-methylvalerate and 0.740 g (24 mmol) of 60% sodium hydride.

20 m.p.: 132°C

MS (ESI pos): $m/z = 297$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO- d_6): $\delta = 0.8$ (m, 6H), 1.1-1.4 (m, 2H), 1.9 (m, 1H), 2.1 (s, 3H), 2.4 (dd, 1H), 2.55 (dd, 1H), 7.3-7.5 (m, 4H), 8.2 (s, 1H), 12.2 (s, 1H) ppm.

Example 35-1

6-(2-Methylbutyl)-1-(2-methylphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
(*enantiomer I*)

5 The racemate from Example 35 (380 mg) is separated into the enantiomers by HPLC on a chiral stationary phase [based on the chiral selector poly(N-methacryloyl-L-leucine L-menthylamide), for the principle of preparation and use, see EP-A-379 917; 380 mm x 100 mm column, flow rate 100 ml/min, temperature 24°C, mobile phase: isohexane / ethyl acetate 20:80]. Example 35-1 is the enantiomer I which elutes more quickly under these conditions ($R_t = 15.2$ min).

m.p.: 122°C

10 **Example 35-2**

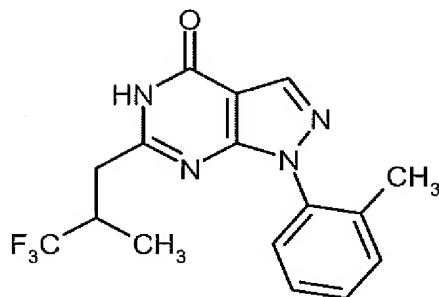
6-(2-Methylbutyl)-1-(2-methylphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
(*enantiomer II*)

15 The racemate from Example 35 (380 mg) is separated into the enantiomers by HPLC on a chiral stationary phase [based on the chiral selector poly(N-methacryloyl-L-leucine L-menthylamide), for the principle of preparation and use, see EP-A-379 917; 380 mm x 100 mm column, flow rate 100 ml/min, temperature 24°C, mobile phase: isohexane / ethyl acetate 20:80]. Example 35-2 is the enantiomer II which elutes more slowly under these conditions ($R_t = 18.1$ min).

m.p.: 122°C

Example 36

20 1-(2-Methylphenyl)-6-(3,3,3-trifluoro-2-methylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (*racemate*)



In analogy to the preparation of Example 1, 216 mg (69% of theory) of the desired product are obtained as a colourless solid starting from 0.2 g (0.92 mmol) of 5-amino-1-(2-methylphenyl)-1H-

pyrazole-4-carboxamide (Example 23A), 0.852 g (4.62 mmol) of ethyl 3-methyl-4,4,4-trifluorobutyrate and 0.129 g (3.24 mmol) of 60% sodium hydride.

m.p.: 160°C

MS (ESI pos): $m/z = 337$ (M+H)⁺

- 5 ¹H-NMR (400 MHz, DMSO-d₆): $\delta = 1.1$ (d, 3H), 2.1 (s, 3H), 2.7 (dd, 1H), 2.85-3.0 (m, 2H), 7.3-7.5 (m, 4H), 8.3 (s, 1H), 12.4 (s, 1H) ppm.

Example 36-1

1-(2-Methylphenyl)-6-(3,3,3-trifluoro-2-methylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (*enantiomer I*)

- 10 The racemate from Example 36 (180 mg) is separated into the enantiomers by HPLC on a chiral stationary phase (column: Chiralpak AD, 250 mm x 20 mm; flow rate: 20 ml/min; temperature: 24°C; mobile phase: isohexane / isopropanol 92:8). Example 36-1 is the enantiomer I which elutes more quickly under these conditions ($R_t = 10.37$ min).

m.p.: 154°C

15 **Example 36-2**

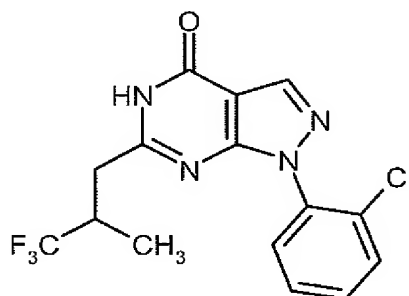
1-(2-Methylphenyl)-6-(3,3,3-trifluoro-2-methylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (*enantiomer II*)

- 20 The racemate from Example 36 (180 mg) is separated into the enantiomers by HPLC on a chiral stationary phase (column: Chiralpak AD, 250 mm x 20 mm; flow rate: 20 ml/min; temperature: 24°C; mobile phase: isohexane / isopropanol 92:8). Example 36-2 is the enantiomer II which elutes more slowly under these conditions ($R_t = 11.73$ min).

m.p.: 153°C

Example 37

1-(2-Chlorophenyl)-6-(3,3,3-trifluoro-2-methylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (*racemate*)



- 5 In analogy to the preparation of Example 1, 321 mg (69% of theory) of the desired product are obtained as a colourless solid starting from 0.3 g (1.27 mmol) of 5-amino-1-(2-chlorophenyl)-1H-pyrazole-4-carboxamide (Example 27A), 1.17 g (6.34 mmol) of ethyl 3-methyl-4,4,4-trifluorobutyrate and 0.254 g (6.34 mmol) of 60% sodium hydride.

m.p.: 166°C

- 10 MS (ESI pos): $m/z = 357 (M+H)^+$

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 1.1$ (d, 3H), 2.7 (dd, 1H), 2.85-3.0 (m, 2H), 7.5-7.8 (m, 4H), 8.3 (s, 1H), 12.4 (s, 1H) ppm.

Example 37-1

- 15 1-(2-Chlorophenyl)-6-(3,3,3-trifluoro-2-methylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (*enantiomer I*)

The racemate from Example 37 (240 mg) is separated into the enantiomers by HPLC on a chiral stationary phase (column: Chiralpak AD, 250 mm x 20 mm; flow rate: 20 ml/min; temperature: 24°C; mobile phase: isohexane / isopropanol 92:8). Example 37-1 is the enantiomer I which elutes more quickly under these conditions ($R_t = 11.92$ min).

- 20 m.p.: 220°C

Example 37-2

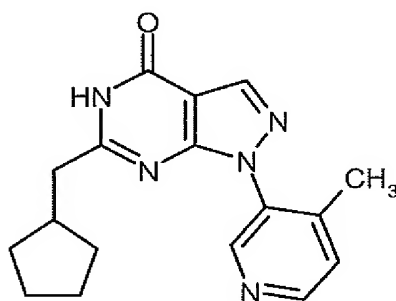
1-(2-Chlorophenyl)-6-(3,3,3-trifluoro-2-methylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (*enantiomer II*)

The racemate from Example 37 (240 mg) is separated into the enantiomers by HPLC on a chiral stationary phase (column: Chiralpak AD, 250 mm x 20 mm; flow rate: 20 ml/min; temperature: 24°C; mobile phase: isohexane / isopropanol 92:8). Example 37-2 is the enantiomer II which elutes more slowly under these conditions II ($R_t = 12.67$ min).

5 m.p.: 218°C

Example 38

6-Cyclopentylmethyl-1-(4-methylpyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



10 In analogy to the preparation of Example 1, 102 mg (73% of theory) of the desired product are obtained as a colourless solid starting from 0.1 g (0.45 mmol) of 5-amino-1-(4-methylpyridin-3-yl)-1H-pyrazole-4-carboxamide (Example 35A), 0.353 g (2.26 mmol) of ethyl cyclopentylacetate and 0.09 g (2.26 mmol) of 60% sodium hydride.

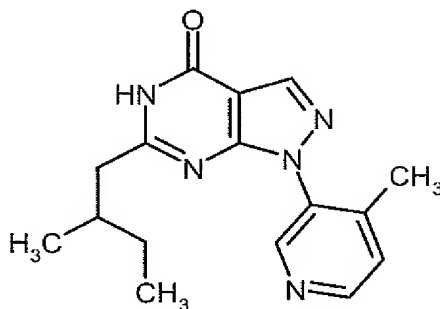
m.p.: 206°C

MS (ESI pos): $m/z = 310$ ($M+H$)⁺

15 ¹H-NMR (400 MHz, DMSO- d_6): $\delta = 1.1$ -1.8 (m, 8H), 2.2 (s, 3H), 2.22 (m, 1H), 2.6 (d, 2H), 7.5 (d, 1H), 8.3 (s, 1H), 8.6 (m, 2H), 12.3 (s, 1H) ppm.

Example 39

6-(2-Methylbutyl)-1-(4-methylpyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
(racemate)



- 5 In analogy to the preparation of Example 1, 186 mg (68% of theory) of the desired product are obtained as a colourless solid starting from 0.2 g (0.92 mmol) of 5-amino-1-(4-methylpyridin-3-yl)-1H-pyrazole-4-carboxamide (Example 35A), 0.677 g (4.6 mmol) of ethyl 3-methylvalerate and 0.184 g (4.6 mmol) of 60% sodium hydride.

m.p.: 149°C

- 10 MS (ESI pos): $m/z = 298$ ($M+H$)⁺

¹H-NMR (400 MHz, DMSO-d₆): $\delta = 0.8$ (m, 6H), 1.1-1.4 (m, 2H), 1.9 (m, 1H), 2.2 (s, 3H), 2.4 (dd, 1H), 2.6 (dd, 1H), 7.5 (d, 1H), 8.3 (s, 1H), 8.6 (m, 2H), 12.25 (s, 1H) ppm.

Example 39-1

6-(2-Methylbutyl)-1-(4-methylpyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

- 15 (*enantiomer I*)

The racemate from Example 39 (160 mg) is separated into the enantiomers by HPLC on a chiral stationary phase [based on the chiral selector poly(N-methacryloyl-L-leucine L-menthylamide), for the principle of preparation and use, see EP-A-379 917; 380 mm x 75 mm column, flow rate 100 ml/min, temperature 24°C, mobile phase: isohexane / ethyl acetate 30:70]. Example 39-1 is the
20 enantiomer I which elutes more quickly under these conditions.

m.p.: 149°C

$R_t = 7.25$ min [chiral selector poly(N-methacryloyl-L-leucine L-menthylamide), 250 mm x 4.6 mm column; flow rate 1 ml/min; temperature 24°C; mobile phase ethyl acetate].

Example 39-2

6-(2-Methylbutyl)-1-(4-methylpyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
(*enantiomer II*)

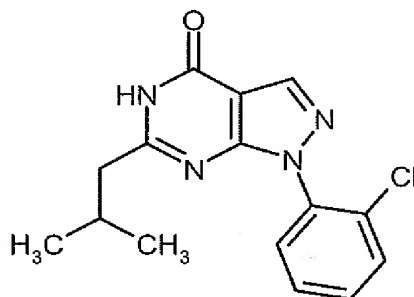
- 5 The racemate from Example 39 (160 mg) is separated into the enantiomers by HPLC on a chiral stationary phase [based on the chiral selector poly(N-methacryloyl-L-leucine L-menthylamide), for the principle of preparation and use, see EP-A-379 917; 380 mm x 75 mm column, flow rate 100 ml/min, temperature 24°C, mobile phase: isohexane / ethyl acetate 30:70]. Example 39-2 is the enantiomer I which elutes more slowly under these conditions.

m.p.: 148°C

- 10 R_t = 8.0 min [chiral selector poly(N-methacryloyl-L-leucine L-menthylamide), 250 mm x 4.6 mm column; flow rate 1 ml/min; temperature 24°C; mobile phase ethyl acetate].

Example 40

1-(2-Chlorophenyl)-6-(2-methylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



- 15 In analogy to the preparation of Example 1, 57 mg (45% of theory) of the desired product are obtained as a colourless solid starting from 0.1 g (0.42 mmol) of 5-amino-1-(2-chlorophenyl)-1H-pyrazole-4-carboxamide (Example 27A), 0.344 g (2.96 mmol) of ethyl 3-methylbutyrate and 0.059 g (1.48 mmol) of 60% sodium hydride.

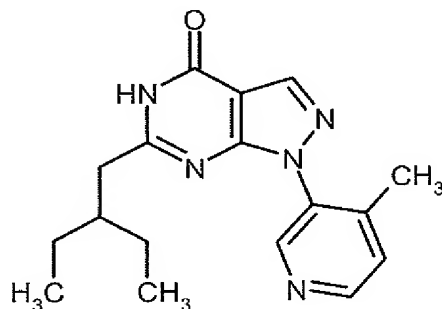
m.p.: 204°C

- 20 MS (ESI pos): m/z = 303 ($M+H$)⁺

¹H-NMR (200 MHz, DMSO-*d*₆): δ = 0.9 (d, 6H), 2.05 (m, 1H), 2.45 (d, 2H), 7.5-7.8 (m, 4H), 8.3 (s, 1H), 12.3 (s, 1H) ppm.

Example 41

6-(2-Ethylbutyl)-1-(4-methylpyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



- In analogy to the preparation of Example 1, 56 mg (49% of theory) of the desired product are obtained as a colourless solid from 0.08 g (0.37 mmol) of 5-amino-1-(4-methylpyridin-3-yl)-1H-pyrazole-4-carboxamide (Example 35A), 0.303 g (1.84 mmol) of ethyl 3-ethylvalerate and 0.074 g (1.84 mmol) of 60% sodium hydride.

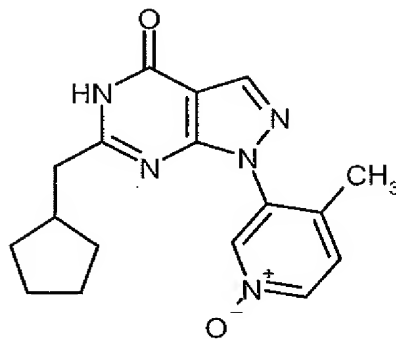
m.p.: 143°C

MS (ESI pos): $m/z = 312 (M+H)^+$

- ¹H-NMR (200 MHz, DMSO- d_6): $\delta = 0.8$ (t, 6H), 1.3 (m, 4H), 1.8 (m, 1H), 2.2 (s, 3H), 2.5 (d, 2H), 7.5 (d, 1H), 8.3 (s, 1H), 8.6 (m, 2H), 12.3 (s, 1H) ppm.

Example 42

6-Cyclopentylmethyl-1-(4-methyl-1-oxidopyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



15

48 mg (70% purity, 0.195 mmol) of meta-chloroperbenzoic acid are added to a solution of 40 mg (0.13 mmol) of 6-cyclopentylmethyl-1-(4-methylpyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Example 38) in 2 ml of dichloromethane at room temperature and stirred

overnight. The mixture is then stirred at 40°C for 1.5 h until the conversion is complete according to a check of the reaction (TCL). For working up, saturated sodium bicarbonate solution is added, and the mixture is extracted three times with dichloromethane. The combined organic phases are dried over sodium sulphate and concentrated. The crude product is purified by preparative HPLC.

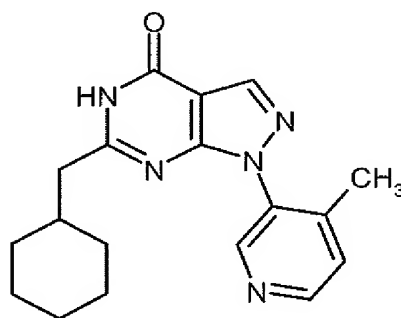
5 32 mg (76% of theory) of the desired product are obtained as a colourless solid.

MS (ESI pos): $m/z = 310 (M+H)^+$

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 1.1\text{--}1.8$ (m, 8H), 2.2 (s, 3H), 2.22 (m, 1H), 2.6 (d, 2H), 7.5 (d, 1H), 8.3 (s, 1H), 8.6 (m, 2H), 12.3 (s, 1H) ppm.

Example 43

10 6-Cyclohexylmethyl-1-(4-methylpyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



In analogy to the preparation of Example 1, 68 mg (73% of theory) of the desired product are obtained as a colourless solid starting from 0.08 g (0.37 mmol) of 5-amino-1-(4-methylpyridin-3-yl)-1H-pyrazole-4-carboxamide (Example 35A), 0.32 g (1.84 mmol) of ethyl cyclohexylacetate and
15 0.074 g (1.84 mmol) of 60% sodium hydride.

m.p.: 206°C

MS (ESI pos): $m/z = 324 (M+H)^+$

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 0.8\text{--}1.3$ (m, 6H), 1.5-1.9 (m, 5H), 2.2 (s, 3H), 2.5 (d, 2H), 7.5 (d, 1H), 8.3 (s, 1H), 8.6 (m, 2H), 12.25 (s, 1H) ppm.

20 The compounds of the invention can be converted into pharmaceutical preparations in the following ways:

Tablet:

Composition:

100 mg of the compound of the invention, 50 mg of lactose (monohydrate), 50 mg of maize starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Ludwigshafen, Germany) and 2 mg
5 of magnesium stearate.

Tablet weight 212 mg, diameter 8 mm, radius of curvature 12 mm.

Production:

A mixture of compound of the invention, lactose and starch is granulated with a 5% strength solution (m/m) of the PVP in water. The granules are dried and mixed with the magnesium stearate
10 for 5 minutes. This mixture is compressed in a conventional tablet press (see above for format of the tablet). A guideline compressive force for the compression is 15 kN.

Suspension which can be administered orally:

Composition:

1000 mg of the compound of the invention, 1000 mg of ethanol (96%), 400 mg of Rhodigel®
15 (xanthan gum from FMC, Pennsylvania, USA) and 99 g of water.

10 ml of oral suspension correspond to a single dose of 100 mg of the compound of the invention.

Production:

The Rhodigel is suspended in ethanol, and the compound of the invention is added to the suspension. The water is added while stirring. The mixture is stirred for about 6 h until the
20 swelling of the Rhodigel is complete.

Solution which can be administered orally:

Composition:

500 mg of the compound of the invention, 2.5 g of polysorbate and 97 g of polyethylene glycol 400. 20 g of oral solution correspond to a single dose of 100 mg of the compound of the invention.

Production:

The compound of the invention is suspended in a mixture of polyethylene glycol and polysorbate with stirring. The stirring process is continued until the compound of the invention has completely dissolved.

5 i.v. solution:

The compound of the invention is dissolved in a concentration below the saturation solubility in a physiologically tolerated solvent (e.g. isotonic saline, 5% glucose solution and/or 30% PEG 400 solution. The solution is sterilized by filtration and filled sterile and pyrogen-free injection containers.

10 Solution which can be administered intravenously:

Composition:

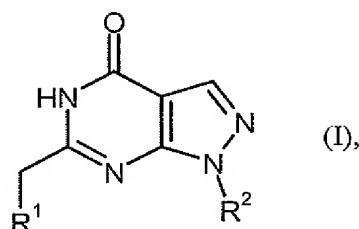
1 mg of the compound of the invention, 15 g of polyethylene glycol 400 and 250 g of water for injection.

Production:

- 15 The compound of the invention is dissolved together with polyethylene glycol 400 in the water with stirring. The solution is sterilized by filtration (pore diameter 0.22 μm) and used to fill heat-sterilized infusion bottles under aseptic conditions. These are closed with infusion stoppers and crimped caps.

Patent Claims

1. Compounds of the formula



in which

- 5 R¹ is C₁-C₈-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl or C₃-C₈-cycloalkyl, where C₁-C₈-alkyl is optionally substituted by oxo, and
where C₁-C₈-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl and C₃-C₈-cycloalkyl are optionally substituted by up to 3 radicals independently of one another selected
10 from the group of C₁-C₆-alkyl, C₁-C₆-alkoxy, hydroxycarbonyl, cyano, amino, nitro, hydroxy, C₁-C₆-alkylamino, halogen, trifluoromethyl, trifluoromethoxy, C₆-C₁₀-arylcarbonylamino, C₁-C₆-alkylcarbonylamino, C₁-C₆-alkylaminocarbonyl, C₁-C₆-alkoxycarbonyl, C₆-C₁₀-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C₁-C₆-alkylsulphonylamino, C₁-C₆-alkylsulphonyl, C₁-C₆-alkylthio,

where

- C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkylamino, C₆-C₁₀-arylcarbonylamino, C₁-C₆-alkylcarbonylamino, C₁-C₆-alkylaminocarbonyl, C₁-C₆-alkoxycarbonyl, C₆-C₁₀-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C₁-C₆-alkylsulphonylamino, C₁-C₆-alkylsulphonyl and C₁-C₆-alkylthio are optionally substituted by one to three radicals independently of one another selected from the group of hydroxy, cyano, halogen, trifluoromethyl, trifluoromethoxy, hydroxycarbonyl and a group of the formula -NR³R⁴,

where

- 25 R^3 and R^4 are independently of one another hydrogen or C_1 - C_6 -alkyl,

or

R^3 and R^4 together with the nitrogen atom to which they are bonded are 5- to 8-membered heterocyclyl,

R^2 is phenyl or heteroaryl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, trifluoromethoxy, amino, nitro, hydroxy, C_1 - C_6 -alkylamino, halogen, C_6 - C_{10} -arylcarbonylamino, C_1 - C_6 -alkylcarbonylamino, C_1 - C_6 -alkylaminocarbonyl, C_1 - C_6 -alkoxycarbonyl, C_6 - C_{10} -arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1 - C_6 -alkylsulphonylamino, C_1 - C_6 -alkylsulphonyl and C_1 - C_6 -alkylthio,

where C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -alkylamino, C_6 - C_{10} -arylcarbonylamino, C_1 - C_6 -alkylcarbonylamino, C_1 - C_6 -alkylaminocarbonyl, C_1 - C_6 -alkoxycarbonyl, C_6 - C_{10} -arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1 - C_6 -alkylsulphonylamino, C_1 - C_6 -alkylsulphonyl and C_1 - C_6 -alkylthio are optionally substituted by one to three radicals independently of one another selected from the group of hydroxy, cyano, halogen, trifluoromethyl, trifluoromethoxy, hydroxycarbonyl and a group of the formula $-NR^3R^4$,

where

R^3 and R^4 have the meanings indicated above,

and the salts, solvates and/or solvates of the salts thereof.

2. Compounds according to Claim 1, where

R^1 is C_1 - C_8 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl or C_3 - C_8 -cycloalkyl, which are optionally substituted by up to 3 radicals independently of one another selected from the group of C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, hydroxycarbonyl, cyano, amino, nitro, hydroxy, C_1 - C_6 -alkylamino, halogen, C_6 - C_{10} -arylcarbonylamino, C_1 - C_6 -alkylcarbonylamino, C_1 - C_6 -alkylaminocarbonyl, C_1 - C_6 -alkoxycarbonyl, C_6 - C_{10} -arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1 - C_6 -alkylsulphonylamino, C_1 - C_6 -alkylsulphonyl and C_1 - C_6 -alkylthio,

where C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -alkylamino, C_6 - C_{10} -arylcarbonylamino, C_1 - C_6 -alkylcarbonylamino, C_1 - C_6 -alkylaminocarbonyl, C_1 - C_6 -alkoxycarbonyl,

C₆-C₁₀-arylamino-carbonyl, heteroarylamino-carbonyl, heteroarylcarbonylamino, C₁-C₆-alkylsulphonylamino, C₁-C₆-alkylsulphonyl and C₁-C₆-alkylthio are optionally substituted by a radical selected from the group of hydroxy, cyano, halogen, hydroxycarbonyl and a group of the formula -NR³R⁴,

5 where

R³ and R⁴ are independently of one another hydrogen or C₁-C₆-alkyl,

or

R³ and R⁴ together with the nitrogen atom to which they are bonded are 5- to 8-membered heterocyclyl,

10 R² is phenyl or heteroaryl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C₁-C₆-alkyl, C₁-C₆-alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, nitro, hydroxy, C₁-C₆-alkylamino, halogen, C₆-C₁₀-arylcarbonylamino, C₁-C₆-alkylcarbonylamino, C₁-C₆-alkylamino-
15 carbonyl, C₁-C₆-alkoxycarbonyl, C₆-C₁₀-arylamino-carbonyl, heteroarylamino-carbonyl, heteroarylcarbonylamino, C₁-C₆-alkylsulphonylamino, C₁-C₆-alkylsulphonyl, C₁-C₆-alkylthio,

where C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkylamino, C₆-C₁₀-arylcarbonylamino, C₁-C₆-alkylcarbonylamino, C₁-C₆-alkylaminocarbonyl, C₁-C₆-alkoxy-
20 carbonyl, C₆-C₁₀-arylamino-carbonyl, heteroarylamino-carbonyl, heteroarylcarbonylamino, C₁-C₆-alkylsulphonylamino, C₁-C₆-alkylsulphonyl and C₁-C₆-alkylthio are optionally substituted by a radical selected from the group of hydroxy, cyano, halogen, hydroxycarbonyl and a group of formula -NR³R⁴,

25 where

R³ and R⁴ have the meanings indicated above,

and the salts, solvates and/or solvates of the salts thereof.

3. Compounds according to Claims 1 and 2, where

5 R^1 is C_1 - C_5 -alkyl or C_3 - C_6 -cycloalkyl, which are optionally substituted by up to 3 radicals independently of one another selected from the group of C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, hydroxycarbonyl, cyano, amino, hydroxy, C_1 - C_4 -alkylamino, trifluoromethyl, fluorine, chlorine, bromine, C_6 - C_{10} -arylcarbonylamino, C_1 - C_4 -alkylcarbonylamino, C_1 - C_4 -alkylaminocarbonyl, C_1 - C_4 -alkoxycarbonyl, C_6 - C_{10} -arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1 - C_4 -alkylsulphonylamino, C_1 - C_4 -alkylsulphonyl, C_1 - C_4 -alkylthio,

10 where C_1 - C_4 -alkyl and C_1 - C_4 -alkoxy are optionally substituted by a radical selected from the group of hydroxy, cyano, fluorine, chlorine, bromine, hydroxycarbonyl and a group of the formula $-NR^3R^4$,

where

R^3 and R^4 are independently of one another hydrogen or C_1 - C_4 -alkyl,

or

15 R^3 and R^4 together with the nitrogen atom to which they are bonded are 5- to 6-membered heterocyclyl,

20 R^2 is phenyl, pyrimidyl, N-oxidopyridyl or pyridyl, where phenyl is substituted by 1 to 3 radicals and pyrimidyl, N-oxidopyridyl and pyridyl are optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, hydroxy, C_1 - C_4 -alkylamino, fluorine, chlorine, bromine, C_6 - C_{10} -arylcarbonylamino, C_1 - C_4 -alkylcarbonylamino, C_1 - C_4 -alkylaminocarbonyl, C_1 - C_4 -alkoxycarbonyl, C_6 - C_{10} -arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1 - C_4 -alkylsulphonylamino, C_1 - C_4 -alkylsulphonyl, C_1 - C_4 -alkylthio,

25 where C_1 - C_4 -alkyl and C_1 - C_4 -alkoxy are optionally substituted by a radical selected from the group of hydroxy, cyano, fluorine, chlorine, bromine, hydroxycarbonyl and a group of the formula $-NR^3R^4$,

where

R^3 and R^4 have the meanings indicated in Claim 1,

30 and the salts, solvates and/or solvates of the salts thereof.

4. Compounds according to Claims 1 to 3, where R^1 has the meanings indicated in Claims 1 to 3, and

5 R^2 is phenyl, N-oxidopyridyl or pyridyl, where phenyl is substituted by 1 to 3 radicals and pyridyl and N-oxidopyridyl are optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, ethoxy, fluorine and chlorine,

and the salts, solvates and/or solvates of the salts thereof.

5. Compounds according to Claims 1 to 4, where

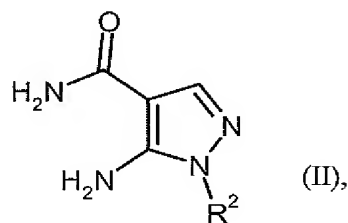
10 R^1 is C_1 - C_5 -alkyl or C_5 - C_6 -cycloalkyl, which are optionally substituted by up to 3 radicals independently of one another selected from the group of C_1 - C_4 -alkyl, trifluoromethyl, fluorine, hydroxy, phenylcarbonylamino, C_1 - C_4 -alkylcarbonylamino, C_1 - C_4 -alkylaminocarbonyl or phenylaminocarbonyl, and

15 R^2 is phenyl, N-oxidopyridyl or pyridyl, where phenyl is substituted by 1 to 3 radicals and pyridyl and N-oxidopyridyl are optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of methyl, ethyl, 2-propyl, trifluoromethyl, methoxy, ethoxy, fluorine and chlorine,

and the salts, solvates and/or solvates of the salts thereof.

6. Process for preparing compounds according to Claim 1, characterized in that

[A] compounds of the formula

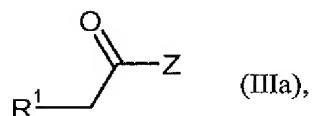


20

in which

R^2 has the meanings indicated in Claim 1,

are converted by reaction with a compound of the formula

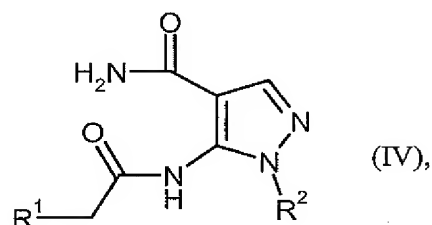


in which R^1 has the meanings indicated in Claim 1,

and

Z is chlorine or bromine,

5 in an inert solvent and in the presence of a base, initially into compounds of the formula



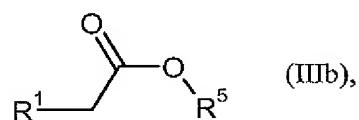
in which

R^1 and R^2 have the meanings indicated in Claim 1,

10 and then cyclized in an inert solvent in the presence of a base to compounds of the formula (I),

or

[B] compounds of the formula (II) are reacted with a compound of the formula



15 in which

R^1 has the meanings indicated in Claim 1,

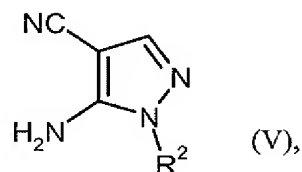
and

R^5 is methyl or ethyl,

in an inert solvent and in the presence of a base, with direct cyclization to (I),

or

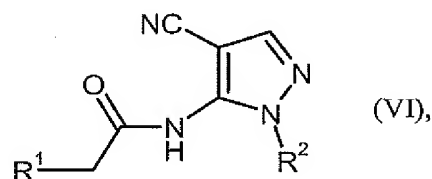
[C] compounds of the formula



5 in which

R^2 has the meanings indicated in Claim 1,

are converted initially by reaction with a compound of the formula (IIIa) in an inert solvent and in the presence of a base into compounds of the formula



10 in which

R^1 and R^2 have the meanings indicated in Claim 1,

and the latter are cyclized in a second step in an inert solvent and in the presence of a base and of an oxidizing agent to (I),

15 and the resulting compounds of the formula (I) are where appropriate reacted with the appropriate (i) solvents and/or (ii) bases or acids to give their solvates, salts and/or solvates of the salts.

7. Compounds according to any of Claims 1 to 5 for the treatment and/or prophylaxis of diseases.
8. Medicament comprising at least one of the compounds according to any of Claims 1 to 5
- 20 and at least one pharmaceutically acceptable, essentially non-toxic carrier or excipient.

9. Use of the compounds according to any of Claims 1 to 5 for producing a medicament for the prophylaxis and/or treatment of impairments of perception, concentration, learning and/or memory.
10. Use according to Claim 9, where the impairment is a consequence of Alzheimer's disease.
- 5 11. Use of the compounds according to any of Claims 1 to 5 for producing a medicament for improving perception, concentration, learning and/or memory.
12. Method for controlling impairments of perception, concentration, learning and/or memory in humans or animals by administering an effective amount of compounds from Claims 1 to 5.
- 10 13. Method according to Claim 12, where the impairment is a consequence of Alzheimer's disease.

6-Cyclymethyl- and 6-alkylmethyl-substituted pyrazolopyrimidines

A b s t r a c t

The invention relates to novel 6-cyclymethyl- and 6-alkylmethyl-substituted pyrazolopyrimidines, process for their preparation and their use for producing medicaments for improving perception, concentration, learning and/or memory.